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CHEMOATTRACTANT RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR

BACKGROUND OF THE INVENTION
Chemokine receptor antagonists or chemokines are a

family of proinflammatory mediators that promote recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of effector cells in chronic inflammation. The chemokines characterized to date are related in primary structure. They share four conserved cysteines, which form disulfide bonds. Based upon this conserved cysteine motif, the family is divided into two

15 main branches, designated as the C-X-C chemokines (α -chemokines), and the C-C chemokines (β -chemokines), in which the first two conserved cysteines are separated by an intervening residue, or adjacent respectively (Baggiolini, M. and Dahinden, C. A., *Immunology Today*, 20 15:127-133 (1994)).

The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β), eotaxin and human monocyte chemoattractant proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and



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(57) Abstract: Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by (I) or (II) and physiologically acceptable salts thereof.

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Secreted), the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β), eotaxin and human monocyte chemoattractant proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and activators of monocytes or lymphocytes but do not appear

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as RANTES and MIP-1 α , have been implicated in a wide range of human acute and chronic inflammatory diseases including respiratory diseases, such as asthma and allergic disorders.

The chemokine receptors are members of a superfamily of G protein-coupled receptors (GPCR) which share structural features that reflect a common mechanism of action of signal transduction (Gerard, C. and Gerard, N.P., *Annu Rev Immunol.*, 12:775-808 (1994); Gerard, C. and Gerard, N. P., *Curr Opin Immunol.*, 6:140-145 (1994)). Conserved features include seven hydrophobic domains spanning the plasma membrane, which are connected by hydrophilic extracellular and intracellular loops. The majority of the primary sequence homology occurs in the hydrophobic transmembrane regions with the hydrophilic regions being more diverse. The first receptor for the C-C chemokines that was cloned and expressed binds the chemokines MIP-1 α and RANTES. Accordingly, this MIP-1 α /RANTES receptor was designated C-C chemokine receptor 1 (also referred to as CCR-1; Neote, K., et al., *Cell*, 72:415-425 (1993); Horuk, R. et al., WO 94/11504, May 26, 1994; Gao, J.-I. et al., *J. Exp. Med.*, 177:1421-1427 (1993)). Three receptors have been characterized which bind and/or signal in response to RANTES: CCR3 mediates binding and signaling of chemokines including eotaxin, RANTES, and MCP-3 (Ponath et al., *J. Exp. Med.*, 183:2437 (1996)), CCR4 binds chemokines including RANTES, MIP-1 α , and MCP-1 (Power, et al., *J. Biol. Chem.*, 270:19495 (1995)), and CCR5 binds chemokines including MIP-1 α , RANTES, and MIP-1 β (Samson, et al., *Biochem.*, 35: 3362-3367 (1996)). RANTES is a chemotactic chemokine for a variety of cell types, including monocytes, eosinophils, and a subset of

T-cells. The responses of these different cells may not all be mediated by the same receptor, and it is possible that the receptors CCR1, CCR4 and CCR5 will show some selectivity in receptor distribution and function between leukocyte types, as has already been shown for CCR3 (Ponath et al.). In particular, the ability of RANTES to induce the directed migration of monocytes and a memory population of circulating T-cells (Schall, T. et al., *Nature*, 347:669-71 (1990)) suggests this chemokine and its receptor(s) may play a critical role in chronic inflammatory diseases, since these diseases are characterized by destructive infiltrates of T cells and monocytes.

Many existing drugs have been developed as antagonists of the receptors for biogenic amines, for example, as antagonists of the dopamine and histamine receptors. No successful antagonists have yet been developed to the receptors for the larger proteins such as chemokines and C5a. Small molecule antagonists of the interaction between C-C chemokine receptors and their ligands, including RANTES and MIP-1 α , would provide compounds useful for inhibiting harmful inflammatory processes "triggered" by receptor ligand interaction, as well as valuable tools for the investigation of receptor-ligand interactions.

SUMMARY OF THE INVENTION

It has now been found that a class of small organic molecules are antagonists of chemokine receptor function and can inhibit leukocyte activation and/or recruitment. An antagonist of chemokine receptor function is a molecule which can inhibit the binding and/or activation of one or more chemokines, including C-C chemokines such

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as RANTES, MIP-1 α , MCP-2, MCP-3 and MCP-4 to one or more chemokine receptors on leukocytes and/or other cell types. As a consequence, processes and cellular responses mediated by chemokine receptors can be inhibited with these small organic molecules. Based on this discovery, a method of treating a disease associated with aberrant leukocyte recruitment and/or activation is disclosed as well as a method of treating a disease mediated by chemokine receptor function. The method comprises administering to a subject in need an effective amount of a compound or small organic molecule which is an antagonist of chemokine receptor function. Compounds or small organic molecules which have been identified as antagonists of chemokine receptor function are discussed in detail hereinbelow, and can be used for the manufacture of a medicament for treating or for preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also relates to the disclosed compounds and small organic molecules for use in treating or preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also includes pharmaceutical compositions comprising one or more of the compounds or small organic molecules which have been identified herein as antagonists of chemokine function and a suitable pharmaceutical carrier. The invention further relates to novel compounds which can be used to treat an individual with a disease associated with aberrant leukocyte recruitment and/or activation and methods for their preparation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formula (I). Figure 2 is a schematic showing the preparation of the compounds represented by Compound (VI-b).

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I)

Figure 4 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z is represented by Structural Formula (III) and wherein Ring A and/or Ring B in Z is substituted with - $(O)_z-(CH_2)_t-COO^{20}$, - $(O)_u-(CH_2)_t-OC(O)R^{20}$, - $(O)_v-(CH_2)_t-C(O)-NR^{21}R^{22}$ or - $(O)_w-(CH_2)_t-NHC(O)O-R^{20}$.

Figures 6A-6Z show the structures of exemplary compounds of the present invention.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formula (III) and wherein Ring A or Ring B in Z is substituted with R⁴⁰.

Figure 8A is a schematic showing the preparation of 4-(4-chlorophenyl)-4-fluoropiperidine.

Figure 8B is a schematic showing the preparation of 4-azido-4-(4-chlorophenyl)piperidine.

Figure 8C is a schematic showing the preparation of 4-(4-chlorophenyl)-4-methylpiperidine.

Figure 9A is a schematic showing the preparation of compounds represented by Structural Formulas (I), (VIII) and (VIII) wherein R¹ is an amine.

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Figure 9B is a schematic showing the preparation of compounds represented by Structural Formulas (I), (VIII) and (VIII) wherein Rⁱ is an alkylamine.

Figure 9C is a schematic showing the preparation of 2-(4-chlorophenyl)-1-(N-methyl)ethylamine.

Figure 9D is a schematic showing the preparation of 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane.

Figure 9E is a schematic showing the preparation of 3-(4-chlorophenyl)-1-N-methylaminopropane.

Figure 10A is a schematic showing the preparation of 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-N-methylaminopropane.

Figure 10B is a schematic showing the preparation of 1-(4-chlorobenzoyl)-1,3-propylenediamine.

Figure 10C is a schematic showing three procedures for the preparation of compounds represented by Structural Formulas (I), (VII), (VIII), (IX) and (XI) wherein Z is represented by Structural Formula (III) and wherein Ring A or Ring B in Z is substituted with R⁴⁰. In Figure 10C, R⁴⁰ is represented by -(O)_u-(CH₂)_t-C(O)-NR²¹R²², u is one, t is zero.

Figure 10D is a schematic showing the preparation of 4-(4-chlorophenyl)-4-pyridine.

Figures 11A-11T show the structures of exemplary compounds of the present invention.

Figure 12 is a schematic showing the preparation of compounds of formula (VI-c).

Figure 13 is a schematic showing the preparation of compounds of formula (VI-e).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to small molecule compounds which are modulators of chemokine receptor function. In a preferred embodiment, the small molecule compounds are antagonists of chemokine receptor function. Accordingly, processes or cellular responses mediated by the binding of a chemokine to a receptor can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium [Ca⁺⁺]_i, and/or granule release of proinflammatory mediators.

The invention further relates to a method of treatment, including prophylactic and therapeutic treatments, of a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by the presence of RANTES, MIP-1 α , MCP-2, MCP-3 and/or MCP-4 responsive T cells, monocytes and/or eosinophils, including but not limited to diseases such as arthritis (e.g., rheumatoid arthritis), atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus (e.g., type 1 diabetes mellitus), psoriasis, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, rejection of transplanted organs and tissues (i.e., acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic treatments) with the

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-CO-NR²R⁴, -NRR⁴; or R¹ can be a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M. R¹ is preferably -H or -OH.

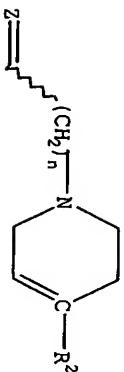
R² is -H, -OH, an acyl group, a substituted acyl group, 5 -NR⁵R⁶, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic

group, -O-(substituted or unsubstituted aromatic group) or 10 -O-(substituted or unsubstituted aliphatic group). R² is preferably an aromatic group or a substituted aromatic group.

R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aromatic group, a benzyl group, an aromatic group, a substituted aromatic group, a substituted benzyl group, a non- 15 aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with 20 the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

In embodiments where M is >CR¹R² and R¹ is a covalent bond between the carbon atom at M and an adjacent carbon atom in the ring which contains M, the antagonist of chemokine function can be represented by Structural Formula (Ia).

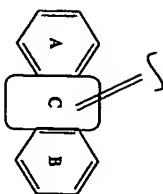


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(Ia)

Z, n and R² are as described in Structural Formula (I).

In one preferred embodiment, Z is a tricyclic ring system comprising two carbocyclic aromatic groups fused to 5 a five, six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. In one example, Z is represented by Structural Formula (II):



(II)

The phenyl rings in Structural Formula (II), labeled 10 with an "A" and "B", are referred to herein as "Ring A" and "Ring B", respectively. The central ring, labeled with a "C", is referred to as "Ring C" and can be, for example, a five, six, seven or eight membered non-aromatic carbocyclic ring (e.g., a cycloheptane or cyclooctane ring) or a non-aromatic heterocyclic ring. When Ring C is a non-aromatic 15 heterocyclic ring, it can contain one or two heteroatoms such as nitrogen, sulfur or oxygen. In particular embodiments, Ring C is when Z is represented by Structural Formula (II), the tricyclic ring system can be connected to the remainder of the molecule by a covalent double bond between a carbon atom in Ring C and the carbon atom which, 20 as depicted in Structural Formula (I), is bonded to Z.

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Ring A and/or Ring B in Structural Formula (II) can be unsubstituted. Alternatively, Ring A and/or Ring B can have one or more substituents. Suitable substituents are as described hereinbelow. In one example, Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)OR^{20}$.

u is zero or one.

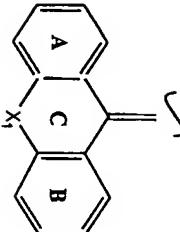
t is an integer, such as an integer from zero to about three, and the methylene group $-(CH_2)_t-$ can be substituted, as described herein for aliphatic groups, or unsubstituted.

R^{20} , R^{21} or R^{22} are independently $-H$, an aliphatic group, a substituted aliphatic group, an aromatic group, a

substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{21} and R^{22} , taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

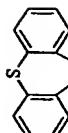
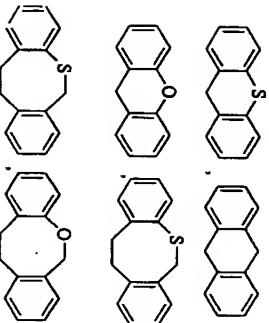
Ring C optionally contains one or more substituents, as described hereinbelow.

Examples of suitable tricyclic ring systems, Z, are provided by Structural Formula (III):

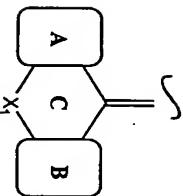
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 20 Other examples of suitable tricyclic ring systems for Z include benzodiazepines, benzoazepines, benzoazines, phenothiazines and groups represented by the following structural formulas:

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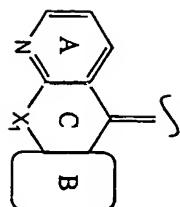
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In another preferred embodiment, Z is a tricyclic ring system comprising two aromatic groups fused to a seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring, wherein at least one of the aromatic groups is a heteroaryl group. In one example, Z is represented by Structural Formula (IV):



(IV)



(IVa).

In this embodiment Ring A and Ring B are independently substituted or unsubstituted, and Ring B is preferably a phenyl group. X₁ and R_c can be as described above for Structural Formula (III).

10 Ring A in Structural Formula (IV) can be a substituted or unsubstituted heteroaryl group. Ring B in Structural

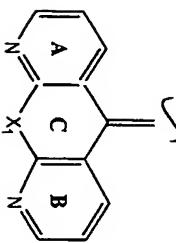
15 Formula (IV) can be a substituted or unsubstituted aromatic group, e.g., a heteroaryl group or carbocyclic aryl group. Suitable substituents are as described hereinbelow. In one example, Ring A and/or Ring B is substituted with

5 - (O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHCO(O)O-R²⁰ as described above. u, t, R²⁰, R²¹, and R²² are as described above. X₁ and R_c can be as described above for Structural Formula (III).

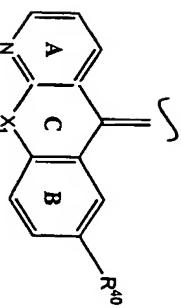
20 In another embodiment of the present invention Z is represented by Structural Formula (IV), wherein Ring A is a pyridyl group and Ring B is an aromatic or heteroaromatic group. In one example, Z is represented by Structural Formula (IVa):

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In another embodiment, both Ring A and Ring B are pyridyl groups, and Z is represented by Structural Formula (IVb):



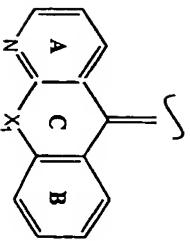
(IVb)



(VI)

Ring A and Ring B can be independently substituted or unsubstituted as described above in Structural Formula (III), and X₁ can be as described above for Structural Formula (III).

In another embodiment of the present invention Z is represented by Structural Formula (V):



(V)

Ring A and Ring B can be independently substituted or unsubstituted as described above for Structural Formula (III), and X₁ can be as described above for Structural Formula (III). Preferably X₁ is -CH₂-O-, -CH₂-CH₂- or -CH₂-S-. R⁴⁰ is a substituent as described herein for aromatic groups. In one embodiment, R⁴⁰ is -OH, -COOH, a halogen, -NO₂, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, -NR²⁴R²⁵, -CONR²⁴R²⁵, -C(=NR⁴⁰)NR²¹R²², -Q-(aliphatic group), -Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰. Q, R²⁰, R²¹, R²², R²⁴, R²⁵, R⁴⁰, u and t are as described herein.

Preferably R⁴⁰ is an aliphatic group, substituted aliphatic group, -O-(aliphatic group) or -O-(substituted

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Ring A and Ring B can be independently substituted or unsubstituted as described above in Structural Formula (II), and X₁ can be as described above for Structural Formula (III).

In a preferred embodiment, Ring B in Structural Formula (V) is substituted para to the carbon atom of Ring B which is bonded to X₁ of Ring C, and Z is represented by Structural Formula (VI):

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aliphatic group). More preferably R^{10} is an -O-alkyl, such as -O-CH₃, -O-C₂H₅, -O-C₃H₇, or -O-C₄H₉.

In another embodiment, R^{10} can be represented by

- (O)_u-(CH_t)_t-C(O)-NR²¹R²², wherein u is one, t is zero, and R²¹ and R²² are as described herein. In this embodiment, R²¹ and R²² can each independently be -H, a substituted or

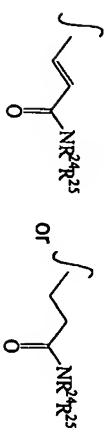
unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, or R²¹ and R²² taken together with the nitrogen atom to which they are bonded form a

10 substituted or unsubstituted nonaromatic heterocyclic ring (e.g., pyrrolidine, piperidine, morpholine).

In another embodiment, R^{10} can be represented by - (O)_u-(CH_t)_t-C(O)-NR²¹R²², wherein u is zero, t is one to about three, and R²¹ and R²² are as described herein.

15 In another embodiment, R^{10} can be represented by - (O)_u-(CH_t)_t-C(O)-NR²¹R²², wherein both u and t are zero, and R²¹ and R²² are as described herein.

In another embodiment, R^{10} is an aliphatic group (e.g., methyl, ethyl, propyl) that is substituted with -NR²⁴R²⁵ or -CONR⁴R⁵, wherein R⁴ and R⁵ are as described herein. For example, R^{10} can be represented by



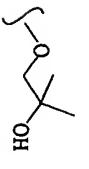
In another embodiment, R^{10} is -O-C(O)-NR²¹R²⁶, wherein R²¹ is as described herein, R²⁶ can be -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O- (substituted or unsubstituted aliphatic

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group), -C(O)-O- (substituted or unsubstituted aromatic group), -S(O)₂- (substituted or unsubstituted aliphatic group), -S(O)₂- (substituted or unsubstituted aromatic group) or R²¹ and R²⁶, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

In additional embodiments, R^{10} can be -S(O)₂-NR²¹R²² or -N-C(O)-NR²¹R²², wherein R²¹ and R²² are as described herein.

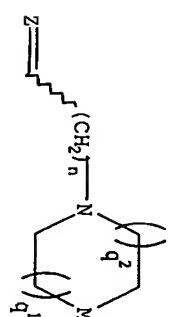
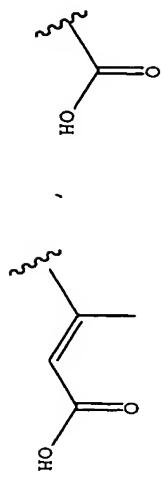
In a preferred embodiment, the chemokine receptor antagonist can be represented by Structural Formula I wherein n is three, M is C(OH)R², R² is a phenyl group or a halophenyl group (e.g., 4-chlorophenyl) and Z is represented by Structural Formula (VI) wherein X₁ is -CH₂-O-. In one example of this embodiment, R^{10} can be -O-(substituted aliphatic group), such as



In particularly preferred embodiments, R^{10} is

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(VII)

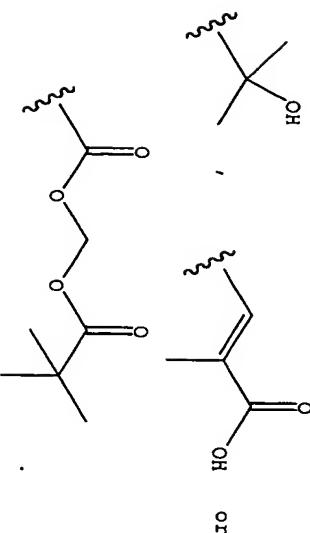
and physiologically acceptable salts thereof.

n is as described in Structural Formula (I). Z is as described herein, preferably as described in Structural Formula (V) or (VI).

M is $>NR^2$, $>CR^1R^2$, $-O-GR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$.

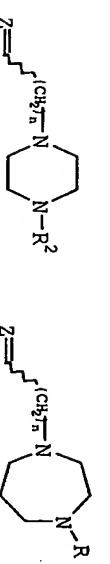
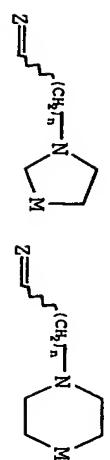
R^1 and R^2 are as described in Structural Formula (I). q^1 is an integer, such as an integer from zero to about three, and q^2 is an integer from zero to about one. The ring containing M can be substituted or unsubstituted.

Thus, the antagonist of chemokine function can be represented by, for example, Structural Formulas (VIIa)-(VIIk):

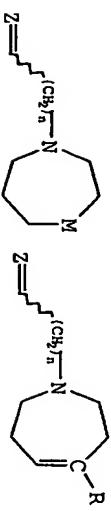


In another embodiment, the antagonist of chemokine activity can be represented by Structural Formula (VII):

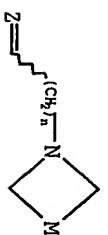
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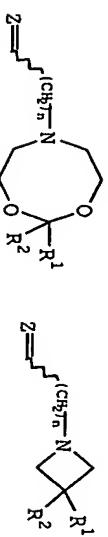
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(VIIb)



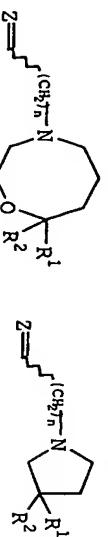
(VIIc)
(VIId)



(VIIe)



(VIIf)



5 and physiologically acceptable salts thereof, wherein Z, n
and M are as described in Structural Formula (VII), and the
ring which contains M is substituted or unsubstituted. The
ring containing M can have one or more suitable
substituents which are the same or different. Suitable
substituents for the ring which contains M and other
nonaromatic heterocyclic rings are as described herein.

10 For example, the ring containing M can be substituted with
a methyl, ethyl, propyl, butyl or oxo group.

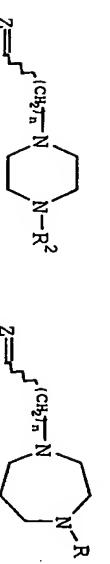
The nitrogen atom in the ring containing M can be a

tertiary nitrogen as depicted in Structural Formula (IV),
or the nitrogen atom can be quaternized with a suitable
15 substituent, such as a C₁ to about C₆ or a C₁ to about C₃,
substituted or unsubstituted aliphatic group. Compounds
which comprise a quaternary nitrogen atom can also contain
a counteranion such as chloride, bromide, iodide, acetate,
perchlorate and the like.

20 The antagonist of chemokine function can be
represented by Structural Formula (VII) wherein the
heterocyclic ring containing M is substituted with a
suitable bivalent group which is bonded to two atoms that
are in the ring, thereby forming a bicyclic moiety.

25 Suitable bivalent groups include, for example, substituted

-23-



(VIIj)
(VIIk)

10 (VIIh)

(VIIIi)

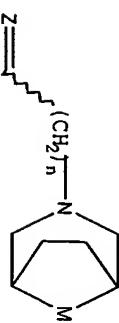
10

-24-

-25-

or unsubstituted bivalent aliphatic groups, such as a C₁-C₆ alkylene group.

The antagonist of chemokine receptor function can comprise a variety of bicyclic moieties. In one embodiment, the antagonist of chemokine receptor function can be represented by Structural Formula (VIII):



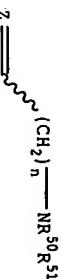
(VIII)

and physiologically acceptable salts thereof.

10 M is >NR², >CR¹R², -O-CR¹R²-O- or -CH₂-CR¹R²-O-.

Preferably, M is >NR² or >CR¹R². R¹ and R² are as described in Structural Formula (I), and n and Z are as described in Structural Formula (VII).

In another embodiment, the antagonist of chemokine receptor function is represented by Structural Formula (IX):



(IX)

and physiologically acceptable salts thereof.

20 Z is as described herein, preferably as described in Structural Formula (V) or (VI).

n is an integer, such as an integer from one to about four. Preferably, n is one, two or three. More preferably

n is two. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for (CH₂)_n.

5 R⁵⁰ and R⁵¹ are each independently -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, a -NR³R⁴, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group or a covalent bond between the nitrogen atom and adjacent carbon atom.

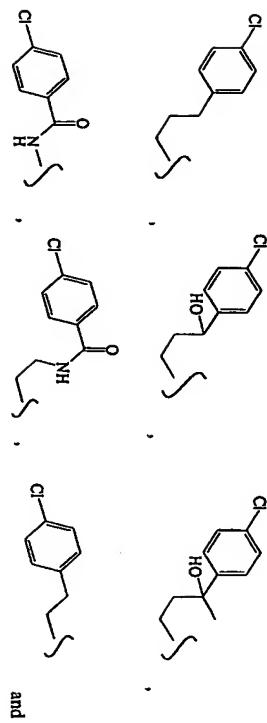
10 R³ and R⁴ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

15 R³ and R⁴ taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

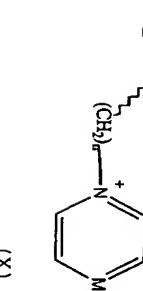
20 In a preferred embodiment R⁵⁰ is a substituted aliphatic group, such as a substituted C₁ to about C₁₂ alkyl group, and R⁵¹ is -H or a substituted or unsubstituted aliphatic group. More preferably, R⁵⁰ is a substituted linear or branched C₂ to about C₆ aliphatic group wherein one or more carbon atoms can be replaced by a heteroatom, such as nitrogen, oxygen or sulfur, and R⁵¹ is -H or a linear or branched C₁ to about C₆ or a C₁ to about C₃ aliphatic group wherein one or more carbon atoms can be replaced by a heteroatom. R⁵⁰ and R⁵¹ can be substituted 25 with one or more suitable substituents, as described herein, preferably an aromatic group(e.g., phenyl,

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4-halophenyl). For example, R³⁰ can be selected from the group consisting of:



and



and physiologically acceptable salts thereof.

Z is a cycloalkyl or non-aromatic heterocyclic ring group fused to one, two or more aromatic rings, wherein each ring in Z is independently substituted or unsubstituted. Preferably, Z is as described in Structural Formula (VI).

The activity of chemokine receptor antagonists represented by Structural Formula IX can be affected by the character of the nitrogen atom to which R³⁰ and R³¹ are bonded. It is believed that compounds in which said nitrogen atom is basic can have potent chemokine receptor antagonist activity. It is known that the basicity of a nitrogen atom can be decreased when the nitrogen atom is bonded to a carbonyl group, sulfonyl group or a sulfinyl group. Therefore, it is preferred that neither R³⁰ nor R³¹

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comprise a carbonyl group, sulfonyl group or sulfinyl group that is directly bonded to the nitrogen atom.

In another aspect, the antagonist of chemokine receptor function is represented by Structural Formula (X):

-28-

-29-

-29-

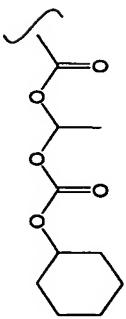
preferably an aromatic group or a substituted aromatic group.

R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

R⁵ and R⁶ taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

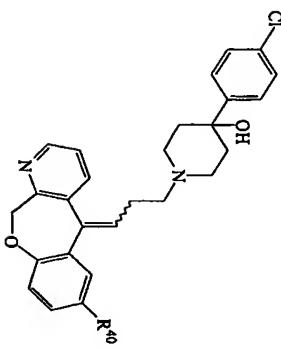
X⁻ is a physiologically acceptable anion. Preferably, X⁻ is Cl⁻ or Br⁻.

The chemokine receptor antagonist described herein can be prepared and administered as active compounds or as prodrugs. Generally, prodrugs are analogues of pharmaceutical agents which can undergo chemical conversion by metabolic processes to become fully active. For example, A prodrug of the invention can be prepared by selecting appropriate groups for R⁴⁰. In one embodiment, a prodrug can be represented by Structural Formula (XI):



wherein, R⁴⁰ is Q-substituted aliphatic group, and the

aliphatic group is substituted with -(O)_u-(CH₂)_t-C(O)OR²⁰,
5 wherein Q is -C(O)O-, u is one, t is zero and R²⁰ is a
cyclic aliphatic group. For example, when the substituted
aliphatic group is a substituted ethyl group, R⁴⁰ can be
represented by:



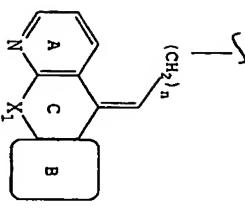
10 Such a prodrug can be converted to an active chemokine receptor antagonist represented by Structural Formula (XI), wherein R⁴⁰ is -COOH.
Another embodiment of the present invention includes novel compounds employed in these methods.

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The compounds disclosed herein can be obtained as E- and Z-configurational isomers. It is expressly pointed out that the invention includes compounds of the E-configuration and the Z-configuration around the double bond connecting Ring C of Z to the remainder of the molecule, and a method of treating a subject with compounds of the E-configuration, the Z-configuration, and mixtures thereof. Accordingly, in the structural formulas presented herein, the symbol:



is used to represent both the E-configuration and the Z-configuration. Preferably Ring A and the alkylene chain bonded to Ring C are in the cis configuration. For example, the compounds can have the configuration of:



10 " "

15 Additionally, certain compounds of the invention may be obtained as different stereoisomers (e.g., diastereomers and enantiomers). It is pointed out that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and a method of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. Again, it is understood that one stereoisomer may be more active than another. The desired isomer can be determined by screening.

10 Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formulas (I) through (XII). Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, citric acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Salts of 20 compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium, calcium and the like.

25 As used herein, aliphatic groups include straight chained, branched or cyclic C₁-C₂₀ hydrocarbons which are completely saturated or which contain one or more units of unsaturation. Preferred aliphatic groups are C₁ to about C₁₀ hydrocarbons. More preferred are C₁ to about C₆ or C₁ to about C₃ hydrocarbons. One or more carbon atoms in an aliphatic group can be replaced with a heteroatom, such as

It is understood that one configuration can have greater activity than another. The desired configuration can be determined by screening for activity, employing the methods described herein.

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nitrogen, oxygen or sulfur. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic C₁-C₂₀ alkyl, alkenyl or alkyanyl groups.

An aminoalkyl group is an alkyl group substituted with -NR²⁴R²⁵, R²⁴ and R²⁵ are as described herein. Preferably the alkyl moiety comprises one to about twelve, more preferably one to about six carbon atoms. The alkyl moiety of an aminoalkyl group can be unsubstituted or substituted as described herein for aliphatic groups. Examples of suitable aminoalkyl groups include aminomethyl,

2-aminoethyl, 3-aminopropyl, 4-aminobutyl, dimethylaminoethyl, diethylaminomethyl, methylaminohexyl, aminoethylengyl and the like.

Aromatic groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heterocyclic aromatic or heteroaryl groups such as N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridazinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Where

these rings are fused, for example, to Ring C, the stated point of attachment can be either of the two fused bonds. Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other rings. Examples include tetrahydronaphthyl, 2-benzothienyl,

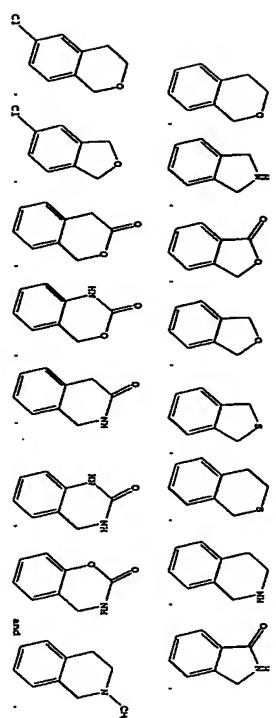
3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 1-isooquinolinyl, 3-quinolinyl, 1-isooindolyl, 3-isoindolyl, acridinyl, 3-benzisoxazolyl, and the like.

Also included within the scope of the term "aromatic group", as it is used herein, is a group in which one or more carbocyclic aromatic rings and/or heteroaryl rings are fused to a cycloalkyl or non-aromatic heterocyclic ring, for example, benzocyclopentane, benzocyclohexane.

Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered and/or fused to another ring, such as a cycloalkyl on aromatic ring.

Examples include 1,3-dioxolan-2-yl, 3-1H-benzimidazol-2-one, 3-1-alkyl-benzimidazol-2-one, 3-1-methyl-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydronaphenyl, 3-tetrahydronaphenyl, 2-morpholino, 2-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidyl, 1-3-alkyl-phthalimidyl, benzoxane, benzopyrrolidine, benzopiperidine, benzoxolane, benzothiolane, benzothiane, tetrahydrofuran-2-one-3-yl, 2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl, 2-oxo-3H-1,2,3,5-oxatriadiazol-4-yl,

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wherein R^{21} and R^{22} , taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

R^{60} is a -H, -OH, -NH₂, an aromatic group or a substituted aromatic group.

t is an integer from zero to about three, and the methylene group, -(CH₂)_t-, can be substituted, as described herein for aliphatic groups, or unsubstituted u is zero or one.

Suitable substituents on an aliphatic group, aromatic group (carbocyclic and heteroaryl), non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, a halogen, azido, -CN, -COOH,

5 electron withdrawing group, a benzyl group, an aryl group or non-aromatic heterocyclic group.

R^{23} is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group.

R^{24} and R^{25} are independently -H, -OH, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group, non-aromatic heterocyclic group or R^{24} and R^{25}

10 taken together with the nitrogen atom to which they are bonded can form a substituted or unsubstituted non-aromatic heterocyclic ring.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aromatic group, an aromatic or substituted aliphatic group, as a substituent.

15 When a non-aromatic ring (carbocyclic aromatic or heteroaryl) is substituted with another ring, the two rings can be fused.

A substituted aliphatic group can also have an oxo group,

20 epoxy group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted

R^{20} , R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group) and

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aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent, which can be the same or different.

Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl and aromatic sulfonyl.

Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, -NO₂, and halogens.

In the structural formulas depicted herein, the single or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:



For example, the corresponding symbol in Structural

20 Formulas (II), (III) and (IV) indicates the double bond by which the central ring of the tricyclic ring system is connected to the remainder of the molecule represented by Structural Formula (I).

A "subject" is preferably a bird or mammal, such as a human, but can also be an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, fowl, pigs,

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horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

An "effective amount" of a compound is an amount which results in the inhibition of one or more processes mediated by the binding of a chemokine to a receptor in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Examples of such processes include leukocyte migration, integrin activation, transient increases in the concentration of intracellular free

10 calcium [Ca²⁺], and granule release of proinflammatory mediators. Alternatively, an "effective amount" of a compound is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compound can range 25 from about 0.1 mg per day to about 100 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day. An antagonist of chemokine receptor function can also be administered in combination with one or more additional therapeutic agents, e.g., theophylline, β-adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents,

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immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone) and the like.

The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral

administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), transdermally, topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral or parenteral administration are preferred modes of administration.

15 The compound can be administered to the individual in conjunction with an acceptable pharmaceutical or physiological carrier as part of a pharmaceutical composition for treatment of HTV infection, inflammatory disease, or the other diseases discussed above.

20 Formulation of a compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for

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encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, et al., "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

5 The activity of compounds of the present invention can be assessed using suitable assays, such as receptor binding assays and chemotaxis assays. For example, as described in the Exemplification Section, small molecule antagonists of RANTES and MIP-1 α binding have been identified utilizing THP-1 cells which bind RANTES and chemotax in response to RANTES and MIP-1 α as a model for leukocyte chemotaxis. Specifically, a high through-put receptor binding assay, which monitors 125 I-RANTES and 125 I-MIP-1 α binding to THP-1 cell membranes, was used to identify small molecule antagonists which block binding of RANTES and MIP-1 α . Compounds of the present invention can also be identified by virtue of their ability to inhibit the activation steps triggered by binding of a chemokine to its receptor, such as chemotaxis, integrin activation and granule mediator release. They can also be identified by virtue of their ability to block RANTES and MIP-1 α mediated HL-60, T-cell, peripheral blood mononuclear cell, and eosinophil, chemotactic response.

15 The compounds disclosed herein can be prepared accordingly to the schemes shown in Figures 1 - 5 and 7. The schemes are described in greater detail below.

Figure 1 shows the preparation of compounds represented by Structural Formula (I). L¹ is PPh₃Cl, PPh₃Br, PPh₃I or (EtO)₂P(O), L² is a suitable leaving group such as halogen, 30 p-toluene sulfonate, mesylate, alkoxy, and phenoxy; Pg is a

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suitable protecting group such as tetrahydropyanyl; and the other symbols are as defined above.

In Step 1 of Figure 1, a Wittig reaction is carried out in a solvent such as ether, or tetrahydrofuran (THF) in the presence of a base such as sodium hydride, n-butyl lithium or lithium diisopropylamide (LDA) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h. Compounds represented by Formula II in Figure 1 can be prepared by methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081, the entire teachings of which are incorporated herein by reference.

In Step 2 of Figure 1, deprotection is carried out with an acid in a solvent such as methanol at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. Alternatively, a compound of represented by Formula V in Figure 1 can be prepared directly from step 1 without isolating an intermediate. The reaction mixture obtained after the work up of the reaction described in step 1 can be dissolved in the solvent and reacted with the acid.

In Step 3 of Figure 1, the hydroxy group can be converted to a leaving group by known methods. Compounds represented by Formula VI in Figure 1 can be prepared by methods disclosed in J. Med. Chem., 1992 (35) 2074-2084 and JP 61/152673.

In Step 4 of Figure 1, an alkylation reaction is carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such

as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 2 shows the preparation of compounds 5 represented by Compound (VI-b). In Step 1 of Figure 2, a Grignard reaction may be carried out in a solvent such as ether, or tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h. Compound VII is available commercially.

In Step 2 of Figure 2, bromination may be carried out with brominating agents such as hydrobromic acid, bromotrimethylsilane or boron tribromide-methyl sulfide complex in a solvent such as acetic acid, dichloromethane or dichloroethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. Figure 3 shows the preparation of compounds represented by Structural Formula (I'). In Figure 3, a reductive amination may be carried out with reducing reagents such as sodium cyanoborohydride, sodium 20 acetoxyporphorohydride or sodium borohydride, as methanol, ethanol, tetrahydrofuran (THF), dichloromethane or dichlorobethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 4 shows the preparation of compounds 25 represented by Structural Formula (II), where in Z is represented by Structural Formulas (III) and wherein Ring A and/or Ring B in Z is substituted with R¹⁰. In Figure 4, the alkylation reaction can be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF)

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in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 5 is a schematic showing the preparation of the compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) and wherein Ring A and/or Ring B in Z is substituted with

$-(O)_u-(CH_2)_v-COOR^{20}$, $-(O)_u-(CH_2)_v-OC(O)R^{20}$,

$-(O)_u-(CH_2)_v-C(O)-NR^2R^2$ or $-(O)_u-(CH_2)_v-NHC(O)O-R^{20}$. In

Figure 5, the hydrolysis reaction may be carried out in a mixture of aqueous alkali metal hydroxide solution and a solvent such as methanol, ethanol, tetrahydrofuran (THF) or dioxane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. The acylation reaction can be carried out using dicyclohexylcarbodiimide (DCC) or (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in a solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or methylene chloride in the presence of a base such as pyridine or triethylamine (when necessary) at temperatures of 0 to 100°C for 5 minutes to 72 h.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) and wherein Ring A or Ring B in Z is substituted with R⁴⁰. I₄ is a suitable leaving group such as halogen or trifluoromethylsulfonate. In Figure 7, a palladium coupling reaction such as Stille coupling, Suzuki coupling, Heck reaction, or carboxylation using carbon monoxide may be carried out using a palladium catalyst such as

tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium chloride, and palladium acetate in a solvent such as tetrahydrofuran (THF), 1,4-dioxane, toluene, dimethylformamide (DMF), or dimethylsulfoxide (DMSO) in the presence of additive (when necessary) such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine, sodium bicarbonate, tetraethylammonium chloride, or lithium chloride at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 10C shows three procedures for the preparation of compounds represented by Structural Formulas (I), (VII), (VIII) and (IX), wherein Z is represented by Structural Formula (III) and wherein Ring A or Ring B in Z is substituted with R⁴⁰. In Figure 10C, R⁴⁰ is represented by $-(O)_u-(CH_2)_v-C(O)-NR^2R^2$, u is one, v is zero. In Figure 10C a compound containing a phenol can be reacted with a carbonate equivalent, such as a carbamoyl chloride (method A), an isocyanate (method B) or an acylimidazole (method C), in the presence of a base such as sodium hydroxide, potassium carbonate or sodium carbonate in a solvent such as dimethylformamide or tetrahydrofuran, at a temperature from 0°C to reflux temperature for a period of about 5 minutes to about 72 hours.

Compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (III) or (IV), X is $-CO-NR_c-$ and R_c is $-(CH_2)_v-COOR^{30}$, $-(CH_2)_v-C(O)-NR^3R^3$ or $-(CH_2)_v-NHC(O)-O-R^{30}$, can be prepared by suitable modification of the scheme shown in Figure 1-5 and 7. One modification utilizes the starting material shown in Figure 1, wherein X is $-CO-NH-$. The amide is then alkylated with

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$L^3-(CH_2)_n-COOR^{30}$, wherein L^3 is a suitable leaving group, using the alkylation procedures described above. The remainder of the synthesis is as described in Figures 1 - 5 and 7.

Figure 12 shows the preparation of compounds of formula (VI-c). The Friedel-Crafts acylation can be carried out using an acid chloride in the presence of a Lewis acid, such as aluminum trichloride or titanium tetrachloride, in a solvent such as dichloromethane,

dichloroethane, nitrobenzene or carbon disulfide. The acylation reaction can be run at a temperature of about room temperature up to the reflux temperature of the chosen solvent, and for a period of about 5 minutes to about 72 hours.

Figure 13 shows the preparation of compounds of formula (VI-e). In Step 1 of Figure 13, a chlorosulfonylation can be carried out using chlorosulfonic acid in a solvent, such as dichloromethane, or in the absence of a solvent at a temperature of about 0°C to about 60°C for a period of about 5 minutes to about 72 hours. In Step 2 of Figure 12, a coupling reaction can be carried out using an amine in the presence of a base, such as triethylamine, in a solvent such as dichloromethane, acetone, ethanol, THF or DMF. The reaction can be carried out at a temperature of about room temperature up to the reflux temperature of the selected solvent, and for a period of about 5 minutes to about 72 hours.

Although Figures 1 - 5, 7, 12 and 13 show the preparation of compounds in which Rings A and B are phenyl rings, analogous compounds with heteroaryl groups for Rings A and B can be prepared by using starting materials with

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heteroaryl groups in the corresponding positions. These starting materials can be prepared according to methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)propyl]piperidin-4-ol

To a solution of 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (described in JP 48-030064) (200mg) in DMF (10mL) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (230mg), potassium carbonate (360mg), and potassium iodide (50mg). The

mixture was stirred at 70°C for 24 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (250mg).

¹H-NMR (CDCl₃) δ: 1.65-2.11(5H,m), 2.32-3.10(8H,m), 3.22-3.67(4H,m), 5.87(1H,t), 7.03-7.44(12H,m). MS m/z: 444(M+1).

Example 2 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 1, but replacing 5-(3-

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bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydrodibenz[b,e]oxepine. ¹H-NMR (CDCl₃) δ: 1.61-2.16 (5H, m), 2.37-2.80 (8H, m), 5.22 (2H, brs), 5.70 (0.6x1H, t), 6.03 (0.4x1H, t), 6.73-6.90 (2H, m), 7.09-7.45 (10H, m). MS m/z: 446 (M+)

Example 3 - Membrane Preparations for Chemokine Binding and Binding Assays

Membranes were prepared from THP-1 cells (ATCC #TIB202). Cells were harvested by centrifugation, washed twice with PBS (phosphate-buffered saline), and the cell pellets were frozen at -70 to -85°C. The frozen pellet was thawed in ice-cold lysis buffer consisting of 5 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid) pH 7.5, 2 mM EDTA (ethylenediaminetetraacetic acid), 5 µg/ml each aprotinin, leupeptin, and chymostatin (protease inhibitors), and 100 µg/ml PMSF (phenyl methane sulfonyl fluoride - also a protease inhibitor), at a concentration of 1 to 5 × 10⁷ cells/ml. This procedure results in cell lysis. The suspension was mixed well to resuspend all of the frozen cell pellet. Nuclei and cell debris were removed by centrifugation of 400 × g for 10 minutes at 4°C. The supernatant was transferred to a fresh tube and the membrane fragments were collected by centrifugation at 25,000 × g for 30 minutes at 4°C. The supernatant was aspirated and the pellet was resuspended in freezing buffer consisting of 10 mM HEPES pH 7.5, 300 mM sucrose, 1µg/ml each aprotinin, leupeptin, and chymostatin, and 10 µg/ml PMSF (approximately 0.1 ml per each 10⁸ cells). All clumps were resolved using a minihomogenizer, and the total

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protein concentration was determined using a protein assay kit (Bio-Rad, Hercules, CA, cat #500-0002). The membrane solution was then aliquoted and frozen at -70 to -85°C until needed. Binding Assays utilized the membranes described above. Membrane protein (2 to 20 µg total membrane protein) was incubated with 0.1 to 0.2 nM ¹²⁵I-labeled RANTES or MIP-1α with or without unlabeled competitor (RANTES or MIP-1α) or various concentrations of compounds. The binding reactions were performed in 60 to 100 µl of a binding buffer consisting of 10 mM HEPES pH 7.2, 1 mM CaCl₂, 5 mM MgCl₂, and 0.5% BSA (bovine serum albumin), for 60 min at room temperature. The binding reactions were terminated by harvesting the membranes by rapid filtration through glass fiber filters (GF/B or GF/C, Packard) which were presoaked in 0.3% polyethyleneimine. The filters were rinsed with approximately 600 µl of binding buffer containing 0.5 M NaCl, dried, and the amount of bound radioactivity was determined by scintillation counting in a Topcount beta-plate counter.

The activities of test compounds are reported in the Table below as IC₅₀ values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ¹²⁵I-RANTES or ¹²⁵I-MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or ¹²⁵I-MIP-1α.

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Table
BIOLOGICAL DATA

Example	IC ₅₀ (μM)
1	<1
2	<1
8	<1
12	<1
17	<10
18	<10
19	<1
21	<1
22	<1
23	<1
24	<10
25	<1
26	<1
27	<1
28	<1
29	<1
30	<1
31	<1
32	<1
33	<1
34	<1
35	<1
36	<1
38	<1
39	<10
40	<1
41	<1
42	<1
43	<10
44	<1
45	<1
46	<1
47	<1
48	<1
49	<1
50	<1
51	<1
52	<1
53	<1
54	<1
55	<1
56	<1
57	<10
59	<1
60	<1
61	<10
62	<10
63	<10
64	<1
65	<1
66	<1000
67	<1
68	<10
69	<1
71	<1
72	<10
73	<10
74	<1000
75	<10
76	<10
77	<1
78	<1
79	<1
80	<1
83	<1000
85	<1
86	>10
89	>10
90	<1
91	<1
111	<1
114	<1
117	<1
118	<1
120	<1
123	<1

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BIOLOGICAL DATA (cont.)

Example	IC ₅₀ (μM)
5	128 <1
	130 <1
	131 <1
10	132 <1
	133 <1
	134 <1
15	135 <1
	138 <1
	139 <1
20	140 >10
	141 <1
	142 <10
25	143 <1
	144 <1
	145 <10
30	146 >10
	147 <10
	148 <10
35	149 <1000
	150 <10
	151 <1
40	152 <1
	153 <1
	154 <1
45	155 <1
	158 <1
	159 <1
50	160 <1
	161 <10
	162 <1
55	163 <1
	166 <10
	167 >1
60	168 1
	172 <1
	173 <1
65	174 <1
	175 <1
	176 <1
70	178 <1

BIOLOGICAL DATA (cont.)

Example	IC ₅₀ (μM)
5	180 <1
	181 <1
	182 <1
10	183 <1
	184 <10
	185 <1000
15	186 <1
	187 <1
	188 >10
20	189 >10
	190 >10
	191 >10
25	192 >10
	193 <1
	194 <1
30	195 <10
	197 <1
	198 <1
35	199 <1
	200 <1
	201 <1
40	203 <1
	204 <1
	205 <1
45	211 <1
	212 <1
	215 <1
50	216 <1
	218 <1
	242 <10
55	248 <10
	249 <1
	262 <1
60	263 <1
	264 <1
	265 <1
65	266 <1
	267 <1
	268 <1
70	269 <1
	270 <1

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BIOLOGICAL DATA (cont.)

Example 8 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-dibenzo[b,e]thiepin-11-ylidene)propyl]piperidin-4-ol

Step 1
11-(3-Bromopropylidene)-6,11-

5 dihydrodibenz[b,e]thiepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxyphrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydrodibenz[b,e]thiepin-11-one.

¹H-NMR (CDCl₃) δ: 2.50-2.64 (2H,m), 3.36-3.47 (3H,m), 4.99 (1H,d), 5.94 (1H,t), 6.98-7.31 (8H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3 but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.65-1.80 (3H,m), 1.95-2.70 (10H,m), 3.35 (1H,d), 4.98 (1H,d), 5.96 (1H,t); 7.09-7.43 (12H,m). MS m/z: 462 (M+1)

Example 12 - 1-[3-(5-Benzyl-6,11-dihydro-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

To a solution 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]piperidin-4-ol hydrochloride (Example 39) (300mg) in DMF (5mL) were added 25 sodium hydride (60% in oil, 200mg), benzyl bromide (0.15mL) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated

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aqueous sodium chloride, and dried with magnesium sulfate.

The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (180mg).

¹H-NMR (CDCl₃) δ: 1.62-1.67(2H,m), 1.99-2.20(3H,m), 2.33-2.65(8H,m), 5.10(1H,d), 5.75(1H,d), 5.94(1H,t), 7.11-7.42(16H,m), 7.91(1H,dd).
MS m/z: 549(M+1)

Example 17 - 1-[3-(5-Carboxymethyl-6,11-dihydro-6-oxo-5H-

10 dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-

15 ethoxycarbonylmethyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl)piperidin-4-ol (Example 18) (1.0g) was solved in 1M hydrogen chloride in diethyl ether and stirred at room temperature for 24 hours. Aqueous sodium hydroxide and ethyl acetate were added to the reaction mixture, the aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (250mg).

¹H-NMR (DMSO-d₆) δ: 1.44-1.61(2H,m), 2.07-2.17(1H,m), 2.35-3.01(9H,m), 4.28(1H,d), 4.59(1H,d), 5.83(1H,t), 7.18-7.71(12H,m).
MS m/z: 517(M+1)

Example 19 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-

10 5-methyl-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl)piperidin-4-ol
The titled compound was prepared by following the procedure of Example 1, but replacing 5-(3-

15 bromopropylidene)-10,11-dihydro-5H-dibenz[a,d]cycloheptene with 11-(3-bromopropylidene)-5-ethoxycarbonylmethyl-6-oxo-5H-

20 dibenz[b,e]azepine.
¹H-NMR (CDCl₃) δ: 1.30(3H,t), 1.64-1.69(2H,m), 1.97-2.10(3H,m), 2.38-2.71(8H,m), 4.27(2H,q), 4.32(1H,d), 4.84(1H,d), 5.88(1H,t), 7.16-7.45(11H,m), 7.88(1H,dd).
MS m/z: 545(M+1)

Example 20 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-

10 dibenz[a,d]cycloheptene-5-ylidene)propyl)piperidin-4-ol
The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-

15 bromopropylidene)-10,11-dihydro-5H-dibenz[a,d]cycloheptene with 5-(3-bromopropylidene)-5H-dibenz[a,d]cycloheptene.

20

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¹H-NMR (CDCl₃) δ: 1.58-1.63 (2H, m), 2.00-2.05 (2H, m), 2.26-2.46 (6H, m), 2.62-2.66 (2H, m), 5.55 (1H, t), 6.85 (2H, s), 7.24-7.40 (12H, m).

MS m/z: 442 (M+1).

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5 Example 22 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-

10 bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydro-2-methoxy-

carbonyldibenz[b,e]oxepine.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H, m), 2.01-2.13 (3H, m), 2.41-2.80 (7H, m), 3.85 (3H, s), 5.40 (2H, brs), 5.73 (0.6x1H, t), 6.09 (0.4x1H, t), 6.76 (0.6x1H, d), 6.82 (0.4x1H, d), 7.21-7.43 (8H, m), 7.73 (1H, dd), 7.87 (0.6x1H, d), 7.97 (0.4x1H, d). MS m/z: 504 (M+1).

Example 24 - 1-[3-(2-Carboxy-1-6,11-

5 dihydridobenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-Chlorophenyl)-1-[3-(6,11-

dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 22, (100mg) in 10 ethanol (3ml) were added 15% sodium hydroxide aqueous solution (0.6ml) and the mixture was heated to reflux for 12 hours. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the reaction mixture, the aqueous layer was separated and 15 neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (80mg).

¹H-NMR (CD₃OD) δ: 1.73-1.79 (2H, m), 2.14-2.19 (2H, m), 2.80-2.93 (3H, m), 3.02-3.11 (3H, m), 3.24-3.29 (2H, m),

20 5.25 (2H, brs), 5.61 (0.7x1H, t), 6.05 (0.3x1H, t), 6.72 (1H, d), 7.22-7.40 (8H, m), 7.52-7.65 (1H, m), 7.75 (0.7x1H, d), 7.80 (0.3x1H, d).

MS m/z: 490 (M+1).

Example 25 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-

25 dimethylaminocarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-

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bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-2-dimethylaminocarbonyl-6,11-dihydrodibenz[b,e]oxepine.

¹H-NMR (CDCl₃) δ: 1.62-1.67 (2H,m), 2.00-2.12 (2H,m), 2.37-5.2.47 (8H,m), 2.89 (6H, s), 5.25 (2H,brs), 5.68 (0.7x1H,t), 6.03 (0.3x1H,t), 6.71 (0.3x1H,d), 6.78 (0.7x1H,d), 7.13-7.40 (10H,m).

MS m/z: 517 (M+1).

Example 26 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxymethyl)dibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

To a solution of (4-chlorophenyl)-1-[3-(6,11-dihydro-2-dihydromethoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

10 added lithium aluminum hydride (1.0M, 0.42mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 hour. Aqueous sodium hydroxide (1M) was added to the reaction mixture to stir for 30 minutes, then ethyl acetate and water was added and brine was added to the mixture. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (95:5) to give the titled compound (20mg).

¹H-NMR (CDCl₃) δ: 1.54 (0.7x6H,s), 1.62 (0.3x6H,s), 1.63-1.70 (2H,m), 2.03-2.10 (3H,m), 2.38-2.49 (3H,m), 2.62-2.82 (4H,m), 5.17 (2H,brs), 5.68 (0.7x1H,t), 6.05 (0.3x1H,t), 6.75 (0.3x1H,d), 6.83 (0.7x1H,d), 7.18-7.43 (10H,m). MS m/z: 504 (M+1).

Example 28 - 4-(4-Chlorophenyl)-1-[3-(2-cyano-6,11-dichloromethane-methanol (10:1) to give the titled compound (90mg).

¹H-NMR (CDCl₃) δ: 1.61-1.66 (2H,m), 1.98-2.03 (2H,m), 2.39-2.48 (3H,m), 2.57-2.79 (6H,m), 4.52 (2H,s), 5.20 (2H,brs), 5.66 (0.8x1H,t), 6.01 (0.2x1H,t), 6.67 (0.2x1H,d), 6.79 (0.8x1H,d), 7.06 (1H,dd), 7.15-7.37 (9H,m).

Example 27 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-(1-hydroxy-1-methyl)ethyl)dibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

5 To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxycarbonyldibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (60mg) in THF (6mL) were added methyImagnesium chloride (3.0M, 0.16mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 2 hour, the reaction mixture was quenched by saturated ammonium aqueous, then ethyl acetate and water was added to the mixture. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (95:5) to give the titled compound (20mg).

25

The titled compound was prepared by following the procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

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with 11-(3-bromopropylidene)-2-cyano-6,11-dihydrodibenz[b,e]oxepin-¹H-NMR (CDCl₃) δ: 1.67-1.72(2H,m), 2.02-2.13(2H,m), 2.37-2.77(8H,m), 5.35(2H,brs), 5.75(0.7x1H,t), 6.07(0.3x1H,t), 6.78(0.3x1H,d), 6.82(0.7x1H,d), 7.25-7.51(10H,m).
 5 MS m/z: 471 (M+1).

Example 29 - 1-[3-(2-Aminomethyl-6,11-

dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(2-cyano-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol (380mg) in EtOH (20mL) were added Raney nickel (50% slurry in water, 60 mg), and the mixture was hydrogenated at 15 psi for 2 hours. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol-aqueous ammonium (95:5:1) to give the titled compound (130mg).

¹H-NMR (CDCl₃) δ: 1.76-1.94(3H,m), 2.18-2.34(2H,m), 2.85-3.10(8H,m), 3.88(2H,s), 5.30(2H,brs), 5.59(1H,t), 6.78(1H,d), 7.13-7.40(10H,m).

MS m/z: 475 (M+1).

Example 30 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-nitrodibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

procedure of example 1, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with 11-(3-bromopropylidene)-6,11-dihydro-2-nitrodibenz[b,e]oxepine.

¹H-NMR (CDCl₃) δ: 1.62-1.67(2H,m), 1.80-2.12(3H,m), 2.28-2.78(8H,m), 5.05(0.3x2H,brs), 5.40(0.7x2H,brs), 5.90(0.7x1H,t), 6.17(0.3x1H,t), 6.82(0.3x1H,d), 6.92(0.7x1H), 7.28-7.41(8H,m), 7.82(1H,dd), 8.15(0.7x1H,d), 8.22(0.3x1H,d).
 5 MS m/z: 491 (M+1).

Example 31 - 1-[3-(2-Amino-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-

dihydro-2-nitrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol (120mg) in EtOH (15mL) were

added tin (II) chloride (190mg), and the mixture was heated to reflux for 1 hour. The was distilled off under reduced pressure. The residue was added ethyl acetate and sodium

aqueous to neutralize. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane-methanol (95:5) to give the titled compound (70mg).

¹H-NMR (DMSO-d₆) δ: 1.54-1.60(2H,m), 1.85-2.00(2H,m), 2.30-2.80(8H,m), 3.88(2H,s), 5.07(2H,brs), 5.66(1H,t), 6.41-6.46(2H,m), 6.59(1H,d), 7.24-7.49(8H,m).
 6 MS m/z: 461 (M+1).

Example 32 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol

Step 1

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11-(3-Bromopropylidene)-6,11-dihydro-2-hydroxydibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 5,6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-one.

¹H-NMR (CDCl₃) δ: 2.69(2H,q), 3.39(2H,t), 5.20(2H,brs), 5.92(1H,t), 6.50-6.81(4H,m), 7.17-7.37(4H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.60-1.75(3H,m), 1.95-2.10(2H,m), 2.35-2.80(8H,m), 5.10(2H,brs), 5.93(1H,t), 6.56(2H,brs), 6.71(1H,brs), 7.11-7.35(8H,m). MS m/z: 462(M+1)

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11-(3-Bromopropylidene)-6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.59-1.65(2H,m), 1.95-2.66(11H,m), 3.75(3H,s), 5.10(2H,brs), 6.03(1H,t), 6.69(2H,brs), 6.82(1H,brs), 7.20-7.40(8H,m).

MS m/z: 476(M+1)

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-hydroxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 32) (260mg) in DMF (5ml) were added sodium hydride (60% in oil, 23mg), ethyl iodide (0.052ml) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

Step 1

11-(3-Bromopropylidene)-6,11-dihydro-2-methoxydibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-one.

¹H-NMR (CDCl₃) δ: 2.74(2H,q), 3.43(2H,t), 3.77(3H,s), 5.10(2H,brs), 6.02(1H,t), 6.70-6.83(3H,m), 7.21-7.38(4H,m). MS m/z: 490(M+1)

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.37(3H,t), 1.60-1.65(2H,m), 1.95-2.08(3H,m), 2.28-75(8H,m), 3.96(2H,q), 5.15(2H,brs), 6.02(1H,t), 6.68(2H,brs), 6.82(1H,brs), 7.19-7.42(8H,m).

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Example 35 - 1-[3-(3-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

3-Bromo-11-(3-bromopropylidene)-6,11-dihydrodibenz[b,e]oxepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxyphrido[2,3-c][1]benzoxepin-5-one with 3-bromo-6,11-dihydrodibenz[b,e]oxepin-11-one.

¹H-NMR (CDCl₃) δ: 2.74(2H,q), 3.43(2H,t), 3.77(3H,s),

5.10(2H,brs), 6.02(1H,t), 6.70-6.83(3H,m), 7.21-7.38(4H,m).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.63-1.70(3H,m), 1.96-2.10(2H,m), 2.32-2.69(8H,m), 5.20(2H,brs), 6.00(1H,t), 6.92-7.00(2H,m), 7.11-7.14(1H,m), 7.24-7.42(8H,m).

MS m/z: 524, 526(M+1)

Example 36 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-ylidene)propyl]piperidine

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol (Example 2)(200mg) in dichloromethane (5ml) were added acetyl chloride (0.06ml), triethylamine (0.19ml) and the mixture was stirred at room temperature for 1 hour. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give the titled compound

20 dihydro-2-methoxydibenz[b,e]oxepin-11-

25 ylidene)propyl)piperidin-4-ol (Example 2) (400mg) in DMF (5ml) were added sodium hydride (60% in oil, 50mg), methyl iodide (0.07ml) and the mixture was stirred at room temperature for 1 hour. Water and ethyl acetate were added

to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (100mg).

¹H-NMR (CDCl₃) δ: 1.98-2.85(12H,m), 2.02(3H,s), 2.93(3H,s), 5.23(2H,brs), 6.01(1H,t), 6.73-6.90(3H,m), 7.11-7.40(9H,m),

MS m/z: 488(M+1)

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Example 38 - 1-[3-(8-Bromo-4,10-dihydrothieno[3,2-c][1]benzoxepin-10-ylidene)propyl]piperidin-4-(4-chlorophenyl)-4-ol

Step 1

5 8-Bromo-10-(3-bromopropylidene)-4,10-

dihydrothieno[3,2-c][1]benzoxepine was prepared by

following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one with 4,10-dihydrothieno[3,2-c][1]benzoxepin-10-one.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 2.84(2H, q), 3.45(2H, t), 5.10(2H, s), 6.11(1H, t), 6.65(1H, d), 7.03-7.08(2H, m), 7.38-7.43(2H, m).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-

15 bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.66-1.75(3H, m), 2.03-2.16(2H, m), 2.40-2.86(8H, m), 5.09(0.7x2H, s), 5.14(0.3x2H, s), 5.90(0.3x1H, t), 6.10(0.7x1H, t), 6.64(0.7x1H, d), 6.75(0.3x1H, d), 6.90(0.3x1H, d), 7.03-7.09(2H, m), 7.21-7.45(6H, m).

20 MS m/z : 532(N+1)

Example 39 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

Step 1

25 11-(3-Bromopropylidene)-6,11-dihydro-6-oxo-5H-dibenzo[b,e]azepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-

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Example 40 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethyl-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

Example 41 - 1-[3-(5-n-Butyl-6,11-dihydro-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.61-1.66(2H, m), 1.97-2.20(3H, m), 2.35-2.68(8H, m), 5.80(1H, t), 7.03-7.53(11H, m), 8.02(1H, dd), 9.27(1H, brs).

MS m/z : 459(M+1)

Example 40 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-ethyl-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing benzyl bromide with ethyl iodide.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.19-1.28(3H, m), 1.63-1.69(2H, m), 1.99-2.16(3H, m), 2.37-2.70(8H, m), 3.77-3.85(1H, m), 4.40-4.48(1H, m), 5.85(1H, t), 7.12-7.45(11H, m), 7.85(1H, dd), 8.02(1H, m).

MS m/z : 487(M+1)

Example 41 - 1-[3-(5-n-Butyl-6,11-dihydro-6-oxo-5H-dibenzo[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-

Step 1

25 of example 45, step 1 and 2, but replacing 5,11-dihydro-7-

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The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with *n*-butyl iodide.

¹H-NMR (CDCl₃) δ: 0.90-0.98 (3H, m), 1.25-2.20 (9H, m), 2.40-2.87 (8H, m), 3.62-3.72 (1H, m), 4.52-4.64 (1H, m), 5.85 (1H, t), 7.16-7.45 (11H, m), 7.88 (1H, dd).

MS m/z: 515 (M+1)

Example 42 - 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-5-(3-hydroxypropyl)-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol

To a solution 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]piperidin-4-ol hydrochloride (Example 39) (500mg) in DMF (8mL) were added sodium hydride (60% in oil, 200mg), 2-(3-

15 bromopropoxy)tetrahydro-2H-pyran (0.5mL) and the mixture

was stirred at room temperature for 6 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

20 The solvent was distilled off under reduced pressure. The residue was solved in 1M hydrogen chloride in diethyl ether and stirred at room temperature for 1 hour. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the

titled compound (250mg).

¹H-NMR (CDCl₃) δ: 1.25-2.87 (15H, m), 3.51-3.56 (2H, m), 3.82 (1H, m), 4.81-4.87 (1H, m), 5.86 (1H, t), 7.16-7.45 (11H, m), 7.82 (1H, dd).

MS m/z: 517 (M+1)

Example 43 - 1-[3-(5-tert-Butoxycarbonylmethyl-6,11-dihydro-6-oxo-5H-dibenz[b,e]azepin-11-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 12, but replacing benzyl bromide with tert-butyl bromoacetate.

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 1.65-1.70 (2H, m), 1.95-

2.10 (3H, m), 2.42-2.75 (8H, m), 4.24 (1H, d), 4.75 (1H, d), 5.88 (1H, t), 7.16-7.46 (11H, m), 7.90 (1H, dd).

MS m/z: 573 (M+1)

Example 44 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1
To a solution of the product of example 45, step 1

20 (4.3g) in dichloroethane (100mL) was added boron tribromide-methyl sulfide complex (19.3g) and the mixture was heated to reflux for 3 hour. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:2) to

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give 5-(3-bromopropylidene)-5,11-dihydro-7-hydroxy [1]benzoxepino[2,3-b]pyridine (3.2g).

¹H-NMR (CDCl₃) δ: 2.72(2H,q), 3.45(2H,t), 5.28(2H,brs), 6.03(1H,t), 6.66-6.80(3H,m), 7.26(1H,dd), 7.58(1H,dd), 8.51(1H,dd).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy

[1]benzoxepino[2,3-b]pyridine with the product of step 1.

¹H-NMR (DMSO-d₆) δ: 1.46-1.51(2H,m), 1.74-1.85(2H,m), 2.29-2.51(8H,m), 5.15(2H,brs), 6.07(1H,t), 6.61-6.70(3H,m), 7.33-7.48(5H,m), 7.73(1H,dd), 8.47(1H,dd), 9.06(1H,s). MS m/z: 463(M+1)

15 Example 45 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

Step 1

To a solution of 5,11-dihydro-7-methoxy

[1]benzoxepino[2,3-b]pyridin-5-one (5.0g) in THF (50ml) was

added 1.1M cyclopropylmagnesium bromide THF solution (25ml) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Aqueous ammonium chloride and ethyl acetate were added to the reaction

mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was filtered and washed with ethyl

acetate-hexane (1:2) to give 5-cyclopropyl-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ol (5.0g).

Step 2

To a solution of the product of step 1 (4.3g) in 5 acetic acid (30ml) was added 48% aqueous HBr (25ml) at 10°C. The reaction mixture was warmed to room temperature, and stirred for 12 hours. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over

Magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine (5.6g).

¹H-NMR (CDCl₃) δ: 2.74(2H,q), 3.46(2H,t), 3.78(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82(3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd).

Step 3

To a solution the product of step 2 (1.1g) in DMF (15ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (0.81g) and potassium carbonate (0.53g) and the mixture was stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting

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with methylene chloride-methanol (10:1) to give the titled compound as major regioisomer (0.86g) and minor one (0.05g).

Major isomer

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.64-1.69(2H,m), 1.91-2.08(3H,s), 2.34-2.69(8H,m), 3.77(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82(3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd).
MS m/z: 477(M+1)

Minor isomer

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.65-1.79(3H,m), 2.01-2.13(2H,m), 2.35-2.76(8H,m), 3.76(3H,s), 5.22(2H,brs), 5.95(1H,t), 6.72-6.80(2H,m), 7.06(1H,d), 7.16(1H,dd), 7.28(2H,d), 7.42(2H,d), 7.66(1H,dd), 8.39(1H,dd).
MS m/z: 477(M+1)

Example 47 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-isopropoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with isopropyl bromide.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.30(6H,d), 1.60-1.70(3H,m), 1.99-2.09(2H,m), 2.33-2.69(8H,m), 4.37-4.48(1H,m), 5.26(2H,brs), 6.06(1H,t), 6.73-6.82(3H,m), 7.21-7.43(5H,m), 7.55(1H,dd), 8.47(1H,dd).

MS m/z: 505(M+1)

Example 48 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

15 The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl bromoacetate.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.28(3H,t), 1.63-1.68(2H,m), 1.97-2.02(3H,m), 2.33-2.68(8H,m), 4.24(2H,q), 4.55(2H,s), 5.26(2H,brs), 6.06(1H,t), 6.73-6.88(3H,m), 7.21-7.42(5H,m), 7.55(1H,dd), 8.44(1H,dd).
MS m/z: 549(M+1)

Example 49 - 4-(4-Chlorophenyl)-1-[3-(7-cyanomethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

25 ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with bromoacetonitrile.

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¹H-NMR (CDCl₃) δ: 1.62-1.67(2H,m), 1.94-2.06(2H,m),

2.21(1H,brs), 2.34-2.66(8H,m), 4.70(2H,s), 5.26(2H,brs),
6.10(1H,t), 6.80(2H,brs), 6.92(1H,brs), 7.22-7.41(5H,m),
7.56(1H,dd), 8.44(1H,dd).

5 MS m/z: 502(M+1)

residue was purified by silica gel chromatography eluting with methylene chloride-methanol (10:1) to give the titled compound (120mg).

¹H-NMR (CDCl₃) δ: 1.64-1.69(2H,m), 1.98-2.10(3H,m), 2.36-
2.79(8H,m), 3.89-3.94(2H,m), 3.99-4.04(2H,m), 5.24(2H,brs),
6.04(1H,t), 6.71-6.84(3H,m), 7.23-7.41(5H,m), 7.54(1H,dd),
8.43(1H,dd).

5 MS m/z: 507(M+1)

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 2-bromoethyl acetate.

¹H-NMR (CDCl₃) δ: 1.65-1.72(3H,m), 1.97-2.09(5H,m), 2.37-

2.70(8H,m), 4.11-4.14(2H,m), 4.37-4.41(2H,m), 5.25(2H,brs),
6.07(1H,t), 6.75-6.84(3H,m), 7.23-7.43(5H,m), 7.56(1H,dd),
8.47(1H,dd).

15 MS m/z: 549(M+1)

Example 52 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-morpholinoethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 4-(2-chloroethyl)morpholine hydrochloride.

15 ¹H-NMR (CDCl₃) δ: 1.62-1.67(2H,m), 1.95-2.08(2H,m), 2.20-

2.67(13H,m), 2.74(2H,t), 3.67-3.71(4H,m), 4.04(2H,t),
5.23(2H,brs), 6.05(1H,t), 6.73-6.82(3H,m), 7.20-7.41(5H,m),
7.53(1H,dd), 8.42(1H,dd).

MS m/z: 576(M+1)

Example 51 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of 1-[3-(7-(2-acetoxyethyl)oxy-5,11-

[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol (Example 50) (140mg) in ethanol (5mL) were added 15% sodium hydroxide aqueous solution (2mL) and the mixture was heated to reflux for 1 hour.

25 Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The

20 Example 53 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1
5-(3-Bromopropylidene)-5,11-dihydro [1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

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¹H-NMR (CDCl₃) δ: 2.71 (2H, q), 3.46 (2H, t), 5.33 (2H, brs), 6.04 (1H, t), 7.01-7.17 (3H, m), 7.29 (1H, dd), 7.56 (1H, dd), 8.53 (1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.66-1.71 (2H, m), 2.00-2.20 (3H, m), 2.36-2.69 (8H, m), 5.34 (2H, brs), 6.10 (1H, t), 6.83-6.96 (3H, m), 7.17-7.44 (6H, m), 7.60 (1H, dd), 8.46 (1H, dd).

MS m/z: 447 (M+1)

¹H-NMR (CDCl₃) δ: 2.71 (2H, q), 3.46 (2H, t), 5.33 (2H, brs), 6.04 (1H, t), 7.01-7.17 (3H, m), 7.29 (1H, dd), 7.56 (1H, dd), 8.53 (1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.64-1.69 (2H, m), 1.90-2.07 (3H, m), 2.30-2.67 (8H, m), 5.30 (2H, brs), 6.08 (1H, t), 7.00-7.07 (2H, m), 7.13 (1H, d), 7.25-7.42 (5H, m), 7.56 (1H, dd), 8.47 (1H, dd).

MS m/z: 525, 527 (M+1)

Step 1

Example 54 - 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

8-Bromo-5-(3-bromopropylidene)-5,11-dihydro-5H-pyrido[2,3-c][2]benzazepin-5-ylidene)propylpiperidin-4-ol

Step 2

5-(3-Bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine was prepared by following the procedure of example 45, step 1 and 2, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 10,11-dihydro-5H-pyrido[2,3-c][2]benzazepin-5,10-dione.

¹H-NMR (CDCl₃) δ: 2.75-2.90 (2H, m), 3.45 (2H, t), 5.92 (1H, t), 7.04-7.70 (5H, m), 8.10 (1H, dd), 8.48 (1H, dd), 10.00 (1H, brs).

Step 2

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.64-1.69 (3H, m), 2.00-2.12 (2H, m), 2.35-2.70 (8H, m), 5.82 (1H, t), 7.08 (1H, dd), 7.23-7.62 (8H, m), 8.04 (1H, dd), 8.32 (1H, dd), 8.76 (1H, brs).

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-79-

MS m/z: 460 (M+1)

Example 56 - 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-11-methyl-10-oxo-5H-pyrido[2,3-c][2]benzazepin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 36, but replacing of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-methoxydibenzo[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol with 5-(3-bromopropylidene)-10,11-dihydro-10-oxo-5H-pyrido[2,3-c][2]benzazepine.

10 ¹H-NMR (CDCl₃) δ: 1.64-1.70 (3H, m), 2.00-2.10 (2H, m), 2.41-2.69 (8H, m), 3.62 (3H, s), 5.82 (1H, t), 7.07 (1H, dd), 7.25-7.54 (8H, m), 7.91 (1H, dd), 8.34 (1H, dd). MS m/z: 474 (M+1)

15 **Example 57 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)ethyl]piperidin-4-ol**

Step 1

To a solution of methyltriphenylphosphonium bromide (2.2g) in THF (20ml) was added 1.6M n-butyl lithium hexane solution (2.9ml) at 0°C for 30 minutes. To the reaction mixture cooled to 0°C was added 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one (1.0g) dropwise as THF solution (5ml), and the mixture was warmed to room temperature, and stirred for 3 hours. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous saturated aqueous sodium chloride, and dried with magnesium

sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5,11-dihydro-7-methoxy-5-methylenepyrido[2,3-c][1]benzoxepine (0.14g).

Step 2

To a solution of DMF (0.54ml) was added phosphorus oxychloride (0.41ml) at 0°C for 10 minutes. To the reaction mixture was added the product of step 1 (210mg) in carbon tetrachloride (5ml) and the mixture was heated to reflux for 5 hours. Aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)acetaldehyde (1.30mg).

20 ¹H-NMR (CDCl₃) δ: 3.77 (0.7x3H, s), 3.79 (0.3x3H, s), 5.31 (2H, s), 6.46 (0.7x1H, d), 6.52 (0.3x1H, d), 6.78-7.40 (4H, m), 7.68 (0.3x1H, dd), 7.78 (0.7x1H, dd), 8.55 (0.7x1H, dd), 8.64 (0.3x1H, dd), 9.62 (0.3x1H, d), 9.79 (0.7x1H, d).

25 **Step 3**

The titled compound was prepared by following the procedure of example 58, step 2, but replacing of 3-(5,11-

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dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propanaldehyde with product of step 2.

¹H-NMR (CDCl₃) δ: 1.64-1.82(2H,m), 1.92-2.22(3H,m), 2.43-2.58(2H,m), 2.79-3.45(6H,m), 3.68(0.3x3H,s),

3.70(0.7x3H,s), 5.24(2H,brs), 6.18(0.7x1H,t),
6.21(0.3x1H,t), 6.72-7.42(8H,m), 7.78(0.3x1H,dd),
7.85(0.7x1H,dd), 8.42(0.7x1H,dd), 8.46(0.3x1H,dd).

MS m/z: 463(M+1).

Example 58 - 4-(4-Chlorophenyl)-1-[4-(5,11-dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)butyl]piperidin-4-ol

Step 1

3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propenaldehyde was prepared by following the procedure of example 57, step 2, but replacing 5,11-dihydro-7-methoxy-5-methylene[1]benzoxepino[2,3-b]pyridine with 5,11-dihydro-7-methoxy-5-(propyl-1-ene)[1]benzoxepino[2,3-b]pyridine (by-product of example 45,

step 3).

¹H-NMR (CDCl₃) δ: 3.78(0.3x3H,s), 3.80(0.7x3H,s), -5.32(2H,brs), 6.34-6.39(1H,m), 6.72-7.38(6H,m), 7.58(0.7x1H,dd), 7.77(0.3x1H,dd), 8.49(0.3x1H,dd), 8.60(0.7x1H,dd), 9.51(0.7x1H,d), 9.54(0.3x1H,d).

Step 3

To a solution of the product of step 2 (8mg) in ethanol (2mL) were added 10% Pd-C (2mg) was stirred under hydrogen (under a balloon) at room temperature for 1 hour. The mixture was filtered through the celite and distilled off under reduced pressure to give the titled compound (6mg). ¹H-NMR (CDCl₃) δ: 1.68-3.0(15H,m), 3.77(3H,s), 5.18-5.35(2H,m), 5.94(0.4H,t, E isomer), 6.06(0.6H,t, Z isomer), 6.65-6.88(3H,m), 7.05-7.73(6H,m), 8.30-8.56(1H,m).

Step 2

To a solution of the product of step 1 (90mg) in dichloromethane (6mL) were added sodium triacetoxborohydride (170mg), 4-(4-chlorophenyl)-4-hydroxypiperidine (70mg) and acetic acid (0.02mL) and the

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Example 59 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-phenyl-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.68-1.73 (2H, m), 2.02-2.15 (3H, m), 2.38-2.72 (8H, m), 3.77 (3H, s), 5.26 (2H, brs), 6.08 (1H, t), 6.72-6.83 (3H, m), 7.21-7.36 (4H, m), 7.46-7.49 (2H, m), 7.58 (1H, dd), 8.46 (1H, dd).

MS m/z: 443 (M+1).

Example 60 - 4-(4-Bromophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-bromophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.65-1.69 (2H, m), 2.00-2.10 (3H, m), 2.37-2.71 (8H, m), 3.76 (3H, s), 5.24 (2H, brs), 6.05 (1H, t), 6.70-6.82 (3H, m), 7.24 (1H, dd), 7.38 (2H, d), 7.44 (2H, s), 7.52 (1H, dd), 8.44 (1H, dd).

MS m/z: 521, 523 (M+1).

MS m/z: 521, 523 (M+1).

25 Example 61 - 1-[3-(5,11-Dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-cyano-4-phenylpiperidine.

¹H-NMR (CDCl₃) δ: 1.42-1.57 (3H, m), 1.62-1.75 (2H, m), 2.22-2.70 (8H, m), 2.79 (2H, s), 3.80 (3H, s), 5.25 (2H, brs), 6.08 (1H, t), 6.73-6.84 (3H, m), 7.18-7.24 (6H, m), 7.57 (1H, dd), 8.50 (1H, dd).

MS m/z: 457 (M+1).

Example 63 - 4-Cyano-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

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¹H-NMR (CDCl₃) δ: 1.97-2.06 (4H, m), 2.37-2.60 (6H, m), 2.85-2.90 (2H, m), 3.79 (3H, s), 5.27 (2H, brs), 6.08 (1H, t), 6.72-6.84 (3H, m), 7.24-7.58 (7H, m), 8.49 (1H, dd).
MS m/z: 452 (M+1).

Example 64 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-phenylpiperidine.

¹H-NMR (CDCl₃) δ: 1.73-1.79 (4H, m), 1.96-2.03 (2H, m), 2.37-2.52 (5H, m), 2.86-2.94 (2H, m), 3.77 (3H, s), 5.26 (2H, brs).

6.08 (1H, t), 6.72-6.83 (3H, m), 7.17-7.31 (6H, m), 7.56 (1H, dd), 8.49 (1H, dd).
MS m/z 426 (M+1).

¹H-NMR (CDCl₃) δ: 1.73-1.79 (4H, m), 1.96-2.03 (2H, m), 2.37-2.52 (5H, m), 2.86-2.94 (2H, m), 3.77 (3H, s), 5.26 (2H, brs).
6.08 (1H, t), 6.72-6.83 (3H, m), 7.17-7.31 (6H, m), 7.56 (1H, dd), 8.49 (1H, dd).
MS m/z 426 (M+1).

Example 65 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-keto-1-benzimidazolinyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.75-1.79 (2H, m), 2.03-2.15 (2H, m), 2.38-2.52 (6H, m), 2.93-2.98 (2H, m), 3.78 (3H, s), 4.30-4.38 (1H, m), 5.30 (2H, brs), 6.10 (1H, t), 6.73-6.84 (3H, m), 7.01-7.03 (3H, m), 7.21-7.28 (2H, m), 7.59 (1H, dd), 8.48 (1H, dd).
MS m/z: 483 (M+1).

¹H-NMR (CDCl₃) δ: 1.68-1.74 (4H, m), 1.96-2.03 (2H, m), 2.36-2.48 (5H, m), 2.89-2.94 (2H, m), 3.77 (3H, s), 5.27 (2H, brs), 6.07 (1H, t), 6.73-6.83 (3H, m), 7.10-7.27 (5H, m), 7.57 (1H, dd), 8.48 (1H, dd).
MS m/z: 461 (M+1).

Example 66 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-piperidinopiperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-piperidinopiperidine.

¹H-NMR (CDCl₃) δ: 1.40-2.00 (12H, m), 2.15-2.60 (9H, m), 2.80-2.92 (2H, m), 3.80 (3H, s), 5.28 (2H, brs), 6.05 (1H, t), 6.75-6.86 (3H, m), 7.30 (1H, dd), 7.55 (1H, dd), 8.46 (1H, dd).
MS m/z 434 (M+1).

Example 67 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-keto-1-benzimidazolinyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.75-1.79 (2H, m), 2.03-2.15 (2H, m), 2.38-2.52 (6H, m), 2.93-2.98 (2H, m), 3.78 (3H, s), 4.30-4.38 (1H, m), 5.30 (2H, brs), 6.10 (1H, t), 6.73-6.84 (3H, m), 7.01-7.03 (3H, m), 7.21-7.28 (2H, m), 7.59 (1H, dd), 8.48 (1H, dd).
MS m/z: 483 (M+1).

Example 68 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine

The titled compound was prepared by following the procedure of example 36, but replacing of

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4-(4-chlorophenyl)-1-[3-(6,11-dihydro-2-**methoxydibenz[b,e]oxepin-11-ylidene)propyl]piperidin-4-ol**
with **1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-****b]pyridin-5-ylidene)propyl]-4-(2-keto-1-
5 benzimidazolinyl)piperidine.****¹H-NMR** (CDCl_3) δ : 1.72-1.76 (2H, m), 2.09-2.14 (2H, m), 2.23-

2.54 (6H, m), 2.91-2.96 (2H, m), 3.38 (3H, s), 3.77 (3H, s), 4.30-

4.37 (1H, m), 5.27 (2H, brs), 6.08 (1H, t), 6.71-6.83 (3H, m),

6.93-7.06 (3H, m), 7.23-7.60 (2H, m), 8.08 (1H, dd), 8.48 (1H, dd).

10 MS m/z: 497 (M+1).**Example 69 - 8-[3-(5,11-Dihydro-7-****methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1-
phenyl-1,3,8-triazaspiro[4,5]decane-4-one****The titled compound was prepared by following the
15 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
1-phenyl-1,3,8-triazaspiro[4,5]decane-4-one.****¹H-NMR** (CDCl_3) δ : 1.65-1.70 (2H, m), 2.36-2.41 (2H, m), 2.53-
2.79 (8H, m), 3.76 (3H, s), 4.70 (2H, s), 5.25 (2H, brs),
20 6.10 (1H, t), 6.71-6.88 (6H, m), 7.21-7.27 (3H, m), 7.58-
7.65 (2H, m), 8.48 (1H, dd).**MS m/z:** 497 (M+1).**Example 70 - 1-[3-(5,11-Dihydro-7-****methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidine****The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(2-pyridinyl)piperazine.****Example 70 - 4-Anilino-4-carbonyl-1-[3-(5,11-dihydro-7-
methoxy[1]benzoxepino[2,3-b]pyridin-5-
25 ylidene)propyl]piperidine****The titled compound was prepared by following the
procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(4-chlorophenyl)-4-hydroxypiperidine with
MS m/z: 430 (M+1).****4-anilino-4-carbamylpiperidine.****¹H-NMR** (CDCl_3) δ : 1.85-1.90 (2H, m), 2.03-2.08 (2H, m), 2.19-

2.46 (6H, m), 2.62-2.67 (2H, m), 3.75 (3H, s), 3.97 (1H, brs),

5.27 (2H, brs), 5.53 (1H, brs), 6.03 (1H, t), 6.60 (2H, d), 6.70-

5 6.85 (4H, m), 7.12-7.25 (4H, m), 7.53 (1H, dd), 8.46 (1H, dd).

MS m/z: 485 (M+1).

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Example 73 - 1-Cyclohexyl-4-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-cyclohexylpiperazine.

¹H-NMR (CDCl₃) δ: 1.12-1.27 (6H, m), 1.74-1.86 (6H, m), 2.18-2.52 (11H, m), 3.76 (3H, s), 5.26 (2H, brs), 6.04 (1H, t), 6.74-6.81 (3H, m), 7.23 (1H, dd), 7.55 (1H, dd), 8.48 (1H, dd). MS m/z: 434 (M+1).

Example 74 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-furoyl)piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 1-(2-furoyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.34-2.48 (8H, m), 3.71-3.74 (7H, s), 5.24 (2H, brs), 6.05 (1H, t), 6.42 (1H, dd), 6.70-6.80 (3H, m), 6.93 (1H, d), 7.23 (1H, dd), 7.42 (1H, d), 7.53 (1H, dd), 8.46 (1H, dd). MS m/z: 446 (M+1).

Example 76 - 4-(2-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-chlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.98-2.08 (2H, m), 2.24 (2H, dt), 2.38-2.78 (9H, m), 3.77 (3H, s), 5.27 (2H, brs), 6.08 (1H, t), 6.82-6.75 (3H, m), 7.28-7.19 (3H, m), 7.33 (1H, dd), 7.49 (1H, dd), 7.58 (1H, dd), 8.40 (0.1H, dd, Z isomer), 8.47 (0.9H, dd, E isomer). MS m/z: 477 (M+1)

Example 75 - 4-(3-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

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4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(4-fluorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-1.72(2H,m), 2.04(2H,dt), 2.22-2.78(9H,m), 3.75(3H,s), 5.26(2H,brs), 6.09(1H,t), 6.70-

5 6.88(3H,m), 7.00(2H,dd), 7.23(1H,dd), 7.42(2H,dd), 7.56(1H,dd), 8.41(1H,dd).

MS m/z: 461(M+1)

Example 78 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(p-tolyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(p-tolyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.65-1.78(2H,m), 2.02(2H,dt), 2.31(3H,s),

2.24-2.75(9H,m), 3.75(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.84(3H,m), 7.13(2H,d), 7.23(1H,dd), 7.34(1H,d),

7.56(1H,dd), 8.43(1H,dd).

MS m/z: 457(M+1)

Example 83 - 4-(5-Chloropyridin-2-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(5-chloropyridin-2-yl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.77-1.82(2H,m), 2.36-2.94(11H,m), 3.77(3H,brs), 5.26(2H,brs), 6.07(1H,t), 6.76-6.84(3H,m),

7.26(1H,dd), 7.57(1H,dd), 8.49-7.48(1H,d), 8.42-8.53(3H,m).

MS m/z: 478(M+1)

Example 85 - 4-(5-Chloro-2-keto-1-benzimidazolinyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(5-chloro-2-keto-1-benzimidazolinyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.68-1.72(2H,m), 2.03-2.60(8H,m), 2.90-3.02(2H,m), 3.78(3H,s), 4.32-4.21(1H,m), 5.29(2H,brs),

5.95(0.1H,t, E isomer), 6.08(0.9H,t, Z isomer), 6.70-6.92(3H,m), 7.02(1H,dd), 7.08-7.20(1H,m), 7.26(1H,dd), 2.02(2H,td), 2.32-2.72(8H,m), 3.76(3H,s), 5.27(2H,brs),

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7.58 (0.9H, dd, 2 isomer), 7.70 (0.1H, dd, E isomer),

8.42 (0.1H, dd, E isomer), 8.48 (0.9H, dd, 2 isomer),

10.5 (1H, s). (NH is not observed in the spectrum)

MS m/z: 517 (M+1)

Example 86 - 4-(p-Chloroanilino)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(p-chloroanilino)piperidine.

¹H-NMR (CDCl₃) δ: 1.20-1.54 (2H, m), 1.85-2.20 (4H, m), 2.24-

2.60 (4H, m), 2.73 (2H, m), 3.18 (1H, m), 3.77 (3H, s),

5.27 (2H, brs), 6.06 (1H, t), 6.47 (2H, m), 6.68-6.90 (3H, m),

7.07 (2H, m), 7.24 (1H, dd), 7.57 (1H, m), 8.48 (1H, dd). NH signal

was not observed.

MS m/z: 476 (M+1)

Example 89 - 1-[3-(5,11-Dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]spiro[isobenzofuran-1(3H), 4'-piperidine]

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

1-(p-tosyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.20-2.54 (11H, m), 2.82-3.10 (4H, m),

3.73 (3H, s), 5.16 (2H, brs), 6.00 (1H, t), 6.66-6.85 (3H, m),

7.21 (1H, dd), 7.31 (2H, m), 7.51 (1H, dd), 7.61 (2H, m),

8.45 (1H, dd).

MS m/z: 506 (M+1)

Example 90 - 1'-(3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl)spiro[isobenzofuran-1(3H), 4'-piperidine]

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

spiro[isobenzofuran-1(3H), 4'-piperidine].

¹H-NMR (CDCl₃) δ: 1.62-1.82 (2H, m), 1.92 (2H, dt), 2.25-

2.85 (8H, m), 3.76 (3H, s), 5.03 (2H, s), 5.30 (2H, brs),

6.11 (1H, t), 6.68-6.90 (3H, m), 7.02-7.34 (5H, m), 7.58 (1H, dd),

8.48 (1H, dd).

MS m/z: 455 (M+1)

Example 91 - 5-Chloro-1'-(3-(5,11-dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]spiro[isobenzofuran-1(3H), 4'-piperidine]

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

2 5-chlorospiro[isobenzofuran-1(3H), 4'-piperidine].

¹H-NMR (CDCl₃) δ: 1.69-1.74 (2H, m), 1.81-1.93 (2H, m),

2.30-2.44 (4H, m), 2.52-2.63 (2H, m), 2.71-2.75 (2H, m),

3.79 (3H, s), 5.00 (2H, s), 5.28 (2H, brs), 6.09 (1H, t),

6.73-6.84 (3H, m), 7.03 (1H, d), 7.17-7.28 (3H, m), 7.58 (1H, dd),

8.49 (1H, dd).

MS m/z: 489 (M+1)

Example 111 - 4-(4-Chlorophenyl)-1-[3-(5,11-

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dihydro[1]benzothiepine[2,3-b]pyridin-5-
ylidene)propyl)piperdin-4-ol

The titled compound was prepared by following the

procedure of example 45, but replacing
5, 11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one

with 5, 11-dihydro[1]benzothiepine[2,3-b]pyridin-5-one.
1H-NMR (CDCl₃) δ: 1.66-1.78 (3H, m), 2.04-2.65 (10H, m),
3.66 (1H, brd), 5.05 (1H, brd), 6.03 (1H, t), 7.04-7.46 (10H, m),
8.44 (1H, dd).

10 MS m/z: 463 (M+1)

Example 114 - 4-(4-Chlorophenyl)-1-[3-(5, 11-dihydro-8-
methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
15 procedure of example 45, but replacing
5, 11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one

with 5, 11-dihydro-8-methoxy[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.66-1.70 (3H, m), 1.98-2.09 (2H, m),
2.34-2.70 (8H, m), 3.75 (3H, s), 5.32 (2H, brs), 6.02 (1H, t),
6.39 (1H, d), 6.51 (1H, dd), 7.19-7.44 (6H, m), 7.57 (1H, dd),
8.49 (1H, dd).
MS m/z: 477 (M+1)

Example 114 - 4-(4-Chlorophenyl)-1-[3-(5, 11-dihydro-8-
methoxy[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, but replacing

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5, 11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one
with

5, 11-dihydro-7-methyl[1]benzoxepino[2,3-b]pyridin-5-one.
1H-NMR (CDCl₃) δ: 1.50 (1H, brs), 1.66-1.70 (2H, m),

1.98-2.10 (2H, m), 2.28 (3H, s), 2.34-2.42 (4H, m),
2.52-2.57 (2H, m), 2.66-2.70 (2H, m), 5.30 (2H, brs), 6.08 (1H, t),
6.76 (1H, d), 6.97 (1H, dd), 7.09 (1H, d), 7.24-7.44 (5H, m),
7.57 (1H, dd), 8.49 (1H, dd).

MS m/z: 461 (M+1)

10 Example 117 - 1-[3-(7-Chloro-5, 11-
dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-
(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the
15 procedure of example 45, but replacing
5, 11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one
with

7-chloro-5, 11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.66-1.71 (3H, m), 2.00-2.10 (2H, m),
2.36-2.44 (4H, m), 2.52-2.57 (2H, m), 2.66-2.70 (2H, m),
5.32 (2H, brs), 6.13 (1H, t), 6.78 (1H, d), 7.11 (1H, dd),
7.26-7.44 (5H, m), 7.58 (1H, dd), 8.51 (1H, dd).
MS m/z: 481 (M+1)

Example 118 - 1-[3-(7-Carboxy-5, 11-
dihydro[1]benzoxepino[2,3-b]pyridin-5-
ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the
procedure of example 45, but replacing

Example 118 - 1-[3-(7-Carboxy-5, 11-
dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-
(4-chlorophenyl)piperidin-4-ol
A mixture of the product of example 169 (500 mg),
potassium acetate (330 mg), palladium(II) diacetate (10

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mg), 1,1'-bis(diphenylphosphino)ferrocene (93 mg), in dimethylsulfoxide (10 ml) was purged with carbon monoxide for 5 minutes and stirred under a carbon monoxide balloon at 60°C for 3 hours. Water was added to the reaction mixture, the precipitation was filtered. The solid were dissolved with ethyl acetate and dilute sodium hydroxide solution. The aqueous layer was separated and neutralized with dilute hydrochloric acid. The precipitation was filtered to give the titled compound (250 mg).

¹H-NMR (DMSO-d₆) δ: 1.45-1.55 (2H,m), 1.75-1.85 (2H,m), 2.36-2.62 (8H,m), 5.42 (2H,brs), 6.21 (1H,t), 6.90 (1H,d), 7.40-7.52 (5H,m), 7.75 (1H,dd), 7.83 (1H,dd), 7.95 (1H,d), 8.56 (1H,dd).
MS m/z: 491 (M+1)

15 Example 120

4-(4-Chlorophenyl)-1-[3-(7-carboxymethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of Example 290 (3.7g) in

methanol (74ml), acetic acid (6ml), and water (37ml) were added sodium periodate (1.7g) in water (15ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture were added amidosulfuric acid (1.2g) and sodium chlorite (0.89g) in water (10ml), and the mixture was stirred at room temperature for 15 minutes. The reaction mixture was distilled off under reduced pressure into half volume. The residue was neutralized with 1N sodium hydroxide. The precipitation was filtered and washed with water to give the titled compound (2.6g).
MS m/z: 491 (M+1)

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¹H-NMR (DMSO-d₆) δ: 1.45-1.50 (2H,m), 1.73-1.82 (2H,m), 2.24-2.50 (8H,m), 3.50 (2H,s), 4.84 (1H,brs), 5.24 (2H,brs), 6.13 (1H,t), 6.74 (1H,d), 7.06 (1H,dd), 7.21 (1H,d), 7.33-7.48 (5H,m), 7.74 (1H,dd), 8.50 (1H,dd).
MS m/z: 532 (M+1)

5 Example 122

4-(4-Chlorophenyl)-1-[3-(7-dimethylaminocarbonylmethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 120.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H,m), 1.95-2.06 (2H,m), 2.31-2.66 (9H,m), 2.93 (3H,s), 3.00 (3H,s), 3.61 (2H,s), 5.29 (2H,brs), 6.09 (1H,t), 6.78 (1H,d), 7.00 (1H,dd), 7.20-7.43 (6H,m), 7.56 (1H,dd), 8.42 (1H,dd).
MS m/z: 532 (M+1)

Example 123

1-[3-(7-(2-Carboxy)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 288.

¹H-NMR (DMSO-d₆) δ: 1.44-1.49 (2H,m), 1.70-1.82 (2H,m), 2.22-2.48 (10H,m), 2.75 (2H,t), 4.82 (1H,brs), 5.23 (2H,brs), 6.14 (1H,t), 6.71 (1H,d), 7.04 (1H,dd), 7.17 (1H,d), 7.33-7.48 (5H,m), 7.72 (1H,dd), 8.49 (1H,dd).
MS m/z: 519 (M+1)

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Example 128 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-propoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with propyl iodide.

¹H-NMR (CDCl_3) δ : 1.03(3H, t), 1.65-1.70(2H, m), 1.78(2H, q), 1.98-2.09(3H, m), 2.37-2.45(4H, m), 2.51-2.56(2H, m), 2.66-2.70(2H, m), 3.88(2H, t), 5.26(2H, brs), 6.08(1H, t), 6.72-6.84(3H, m), 7.23-7.43(5H, m), 7.58(1H, dd), 8.43(1H, dd).

MS m/z: 505(M+1)

Example 130 - 4-(4-Chlorophenyl)-1-[3-(7-cyclopropylmethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with cyclopropylmethyl bromide.

¹H-NMR (CDCl_3) δ : 0.31-0.37(2H, m), 0.60-0.67(2H, m), 1.21-1.28(1H, m), 1.66-1.72(3H, m), 2.01-2.11(2H, m), 2.37-2.71(8H, m), 3.77(2H, d), 5.27(2H, brs), 6.08(1H, t), 6.73-6.86(3H, m), 7.23-7.44(5H, m), 7.58(1H, dd), 8.47(1H, dd). MS m/z: 517(M+1)

Step 1

Example 132 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-triphenylmethyltetrazol-5-yl)methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with (2-triphenylmethyltetrazol-5-yl)methyl chloride.

¹H-NMR (CDCl_3) δ : 1.64-1.70(3H, m), 2.02-2.15(2H, m), 2.35-2.71(8H, m), 5.29(2H, brs), 5.33(2H, s), 6.03(1H, t), 6.77(1H, d), 6.83(1H, dd), 6.96(1H, d), 7.04-7.08(6H, m), 7.23-7.45(14H, m), 7.54(1H, dd), 8.50(1H, dd).

Step 2

A solution of the product of step 1 (530 mg) in acetone (2.5 ml), acetic acid (2.5 ml) and water (2.5 ml) was stirred at 55°C for 30 minutes. The reaction mixture was distilled off under reduced pressure. The residue was washed with methanol to give the titled compound (280 mg).

Example 131 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-dimethylaminoethyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with (2-dimethylaminoethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol.

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¹H-NMR (DMSO-d₆) δ: 1.69-1.74 (2H, m), 1.99-2.09 (2H, m), 2.95-3.14 (8H, mrs), 5.18 (2H, brs), 5.20 (2H, s), 6.14 (1H, t), 6.76 (1H, d), 6.93 (1H, dd), 7.04 (1H, d), 7.39-7.48 (5H, m), 7.78 (1H, dd), 8.52 (1H, dd).

5 MS m/z: 545 (M+1)

Example 133 - 1-[3-(7-Carboxymethyloxy-5,11-

dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of product of example 48 (3.0 g) in 10 methanol (50 mL) was added 1N sodium hydroxide solution (8 mL) and the mixture stirred at room temperature for 1 hour. The reaction mixture was distilled off under reduced pressure. The residue was dissolved with water and neutralized with 1N hydrochloric acid. The precipitation 15 was filtered and washed with water to give the titled compound (2.6 g).

¹H-NMR (DMSO-d₆) δ: 1.48-1.53 (2H, m), 1.76-1.88 (2H, m), 2.32-2.60 (8H, m), 4.60 (2H, s), 5.18 (2H, brs), 6.16 (1H, t), 6.72-6.84 (3H, m), 7.34-7.48 (5H, m), 7.73 (1H, dd), 8.50 (1H, dd).

20 MS m/z: 521 (M+1)

Example 134 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of example 133 (420 mg) in 25 dimethylformamide (17 mL) were added 1-hydroxybenzotriazol hydrate (250 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (310 mg), dimethylamine hydrochloride (270 mg) and triethylamine (0.45 mL), and the

mixture stirred at room temperature for 12 hours. Water and chloroform were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure to give the titled compound (380 mg).

¹H-NMR (CDCl₃) δ: 1.67-1.71 (2H, m), 1.95-2.11 (3H, m), 2.37-2.71 (8H, m), 2.97 (3H, s), 3.08 (3H, s), 4.64 (2H, s), 5.27 (2H, brs), 6.09 (1H, t), 6.74-6.82 (2H, m), 6.93 (1H, d), 7.24-7.44 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).

10 MS m/z: 548 (M+1)

Example 135 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-morpholinocarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine 15 hydrochloride with morpholine.

¹H-NMR (CDCl₃) δ: 1.67-1.71 (2H, m), 1.87 (1H, brs), 2.00-2.11 (2H, m), 2.38-2.71 (8H, m), 3.61-3.68 (8H, m), 4.65 (2H, s), 5.27 (2H, brs), 6.09 (1H, t), 6.74-6.83 (2H, m), 6.90 (1H, d), 7.25-7.44 (5H, m), 7.58 (1H, dd), 8.48 (1H, dd).

20 MS m/z: 590 (M+1)

Example 138 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl-1-methylethyl)oxy[1]benzoxepino[2,3-

25 b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 2-bromoisobutyrate.

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¹H-NMR (CDCl₃) δ: 1.27 (3H, t), 1.56 (6H, s), 1.63-1.71 (3H, m),

2.01-2.10 (2H, m), 2.35-2.70 (8H, m), 4.24 (2H, q), 5.28 (2H, brs),

6.05 (1H, t), 6.67-6.75 (2H, m), 6.87 (1H, d), 7.24-7.44 (5H, m),

7.56 (1H, dd), 8.49 (1H, dd).

5 MS m/z: 577 (M+1)

Example 139 - 1-[3-(7-(1-Carboxy-1-methyl ethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the

10 procedure of example 133, but replacing product of example 48 with product of example 138.

¹H-NMR (DMSO-d₆) δ: 1.45-1.52 (8H, m), 1.79-1.85 (2H, m),

2.28-2.53 (8H, m), 5.19 (2H, brs), 6.07 (1H, t), 6.69-6.73 (2H, m),

6.85 (1H, d), 7.33-7.47 (5H, m), 7.71 (1H, dd), 8.48 (1H, dd).

15 MS m/z: 549 (M+1)

Example 140 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-methoxyphenyl)piperidin-4-ol

The titled compound was prepared by following the

20 procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-methoxyphenyl)-4-hydroxypiperidine.

Example 141 - 4-(4-Cyanophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the

25 procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-methoxyphenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.62-1.75 (2H, m), 2.08 (2H, dt), 2.41-2.76 (9H, m), 3.77 (3H, s), 3.78 (3H, s), 5.26 (2H, brs),

6.06 (1H, t), 6.75-6.87 (5H, m), 7.23 (1H, dd), 7.38 (2H, d),

7.57 (1H, dd), 8.45 (1H, dd).

MS m/z: 473 (M+1)

Example 143 - 1-[3-(5,11-Dihydro-7-

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methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-fluoro-3-methylphenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

5 4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(4-fluoro-3-methylphenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.62-1.75(2H,m), 2.05(1H,brs), 2.09(2H,dt), 2.25(3H,s), 2.30-2.76(8H,m), 3.76(3H,s), 5.26(2H,brs), 5.96(0.1H,t, E isomer), 6.07(0.9H,t, 2 isomer), 6.75-6.89(3H,m), 6.93(1H,t), 7.11-7.20(0.3H,m, E isomer), 7.21-7.35(0.24H,m, Z isomer), 7.56(0.9H,dd, E isomer), 7.67(0.1H, dd, E isomer), 8.38(0.1H,dd, E isomer), 8.45(0.9H,dd, Z isomer).

MS m/z: 475(M+1)

Example 144 - 4-(3,4-difluorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(3,4-difluorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-1.72(2H,m), 1.96(2H,dt), 2.33-2.71(8H,m), 3.73(3H,s), 5.23(2H,brs), 5.94(0.1H,t, E isomer), 6.04(0.9H,t, Z isomer), 8.38-8.36(0.9H,m, Z isomer), 6.68-6.79(3H,m), 6.98-7.38(4H,m), 7.50-7.62(0.9H,m, Z isomer), 7.63-7.68(0.1H,m, E isomer), 8.29-8.32(0.1H,m, E isomer), 8.32-8.44(0.9H,m, Z isomer). OH signal was not observed.

MS m/z: 479(M+1)

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Example 145 - 4-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

5 procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(4-chloro-3-trifluoromethylphenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.62-1.74(2H,m), 2.10(2H,dt), 2.35-2.80(8H,m), 2.42(1H, brs), 3.76(3H,s), 5.26(2H,brs), 6.07(0.9H,t, Z isomer), 6.03(0.1H,t, E isomer), 6.82-6.71(3H,m), 7.24(1H,dd), 7.43(1H,d), 7.56(1.8H,dd, Z isomer), 7.65(0.2H,dd, E isomer) 7.83(1H,d), 8.36(0.1H,dd, E isomer), 8.44(0.9H,dd, Z isomer),

MS m/z: 545(M+1)

Example 146 - 4-(3,5-dichlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

procedure of example 45, step 3, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(3,5-dichlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.58-2.22(5H,m), 2.38-2.77(8H,m), 3.76(3H,s), 5.26(2H,brs), 5.92(0.1H,t, E isomer), 6.07(0.9H,t, Z isomer), 6.83-6.71(3H,m), 7.19-7.42(4H,m), 7.56(0.9H,dd, Z isomer), 7.68(0.1H,dd, E isomer), 8.38(0.1H,dd, E isomer), 8.45(0.9H,dd, Z isomer).

MS m/z: 512(M+1)

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Example 147 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(2-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(2-pyridyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.54-1.65(2H,m), 2.06(2H,dt), 2.07(1H,brs), 2.35-2.62(7H,m), 2.73-2.87(2H,m), 3.78(3H,s), 5.28(2H,brs), 6.08(1H,t), 6.72-6.85(3H,m), 7.14-7.29(2H,m), 7.57(1H,d), 7.70(1H,dd), 8.48(2H,dd). MS m/z: 444(M+1)

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The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-trifluoromethylphenyl)piperidin-4-ol.

¹H-NMR (CDCl₃) δ: 1.64-1.75(2H,m), 2.01(1H,brs), 2.16(2H,dt), 2.38-2.86(8H,m), 3.76(3H,s), 5.26(2H,brs), 6.04(1H,t), 6.72-6.84(3H,m), 7.23(1H,dd), 7.56(5H,m), 8.42(1H,dd). MS m/z: 511(M+1)

Example 148 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(3-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(3-pyridyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.65-1.78(2H,m), 2.08(2H,dt), 2.37-2.88(7H,m), 2.63-2.79(2H,m), 3.78(3H,s), 5.28(2H,brs), 6.02(0.1H,t, E isomer), 6.07(0.9H,t, Z isomer), 6.70-6.84(3H,m), 7.22-7.32(3H,m), 7.56(1H,dd), 7.77(1H,dd), 8.46(0.9H,d), 8.57(0.1H,dd, E isomer), 8.73(1H,dd). MS m/z: 444(M+1)

Example 149 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-pyridyl)piperidin-4-ol.

Example 150 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-trifluoromethylphenyl)piperidin-4-ol

¹H-NMR (CDCl₃) δ: 1.64-1.75(2H,m), 2.01(1H,brs), 4-(4-trifluoromethylphenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-hydroxypiperidine.

¹H-NMR (CDCl₃) δ: 1.64-1.75(2H,m), 2.01(1H,brs), 2.16(2H,dt), 2.38-2.86(8H,m), 3.76(3H,s), 5.26(2H,brs), 6.04(1H,t), 6.72-6.84(3H,m), 7.23(1H,dd), 7.56(5H,m), 8.42(1H,dd). MS m/z: 511(M+1)

Example 151 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)piperidin-4-ol.

¹H-NMR (CDCl₃) δ: 1.58-1.72(2H,m), 2.03(2H,dt), 2.34-2.89(8H,m), 2.96(1H,brs), 3.76(3H,s), 5.25(2H,brs), 6.06(1H,t), 6.72-6.83(3H,m), 7.24(1H,dd), 7.37(2H,dd), 7.56(1H,dd), 8.45(1H,dd), 8.48(2H,dd). MS m/z: 444(M+1)

Example 152 - 4-(4-Chlorophenyl)-1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-pyridyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-pyridyl)piperidin-4-ol.

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¹H-NMR (CDCl₃) δ: 1.62-1.92(4H,m), 1.94-2.18(2H,m), 2.28-2.64(5H,m), 2.99(2H,m), 5.25(2H,brs), 6.00(1H,t), 6.60-6.82(3H,m), 7.02-7.36(5H,m), 7.50(1H,dd), 8.47(1H,dd). OH signal was not observed.

MS m/z: 447(M+1)

Example 152 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.40(3H,t), 1.52-2.14(6H,m), 2.30-

2.57(5H,m), 2.94(2H,m), 4.00(2H,q), 5.28(2H,brs),

6.07(1H,t), 6.68-6.86(3H,m), 7.05-7.36(5H,m), 7.58(1H,m),

8.49(1H,m).

MS m/z: 475(M+1)

Example 153 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 46, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.29(3H,t), 1.56-1.85(4H,m), 1.99(2H,dt),

2.28-2.55(5H,m), 2.91(2H,m), 4.27(2H,q), 4.58(2H,s),

5.28(2H,brs), 6.09(1H,t), 6.68-6.95(3H,m), 7.07-

7.32(5H,m), 7.58(1H,dd), 8.49(1H,dd).

MS m/z: 533(M+1)

Example 154 - 1-[3-(7-(Carboxymethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 153.

¹H-NMR (CD₃OD) δ: 1.82-2.17(4H,m), 2.69(2H,m), 2.86(1H,m), 3.07(2H,m), 3.30(2H,m), 3.57(2H,m), 4.57(2H,s), 5.21(2H,brs), 6.10(1H,t), 6.70-7.04(3H,m), 7.16-

7.38(4H,m), 7.44(1H,m), 7.77(1H,m), 8.47(1H,m). COOH signal was not observed.

MS m/z: 505(M+1)

Example 155 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 154.

¹H-NMR (CDCl₃) δ: 1.58-1.92(4H,m), 2.04(2H,m), 2.30-2.68(5H,m), 2.93(2H,m), 2.98(3H,s), 3.08(3H,s),

4.65(2H,s), 5.28(2H,brs), 6.07(1H,t), 6.70-6.98(3H,m), 7.08-7.36(5H,m), 7.60(1H,m), 8.50(1H,m).

MS m/z: 532(M+1)

Example 156 - 1-[3-(7-(2-Acetoxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

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The titled compound was prepared by following the procedure of example 50, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.55-1.88 (4H, m), 1.90-2.32 (2H, m),
 2.10 (3H, s), 2.28-2.60 (5H, m), 2.82-3.02 (2H, m), 4.14 (2H, dd),
 4.41 (2H, dd), 5.29 (2H, brs), 6.08 (1H, t), 6.72-6.90 (3H, m),
 7.18-7.34 (5H, m), 7.57 (1H, m), 8.50 (1H, m).
 MS m/z: 533 (M+1)

Example 159 - 1-[3-(7-(1-Carboxy-1-methylethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 158.

¹H-NMR (CD₃OD) δ: 1.50 (6H, s), 1.82-2.18 (4H, m), 2.70 (2H, m),
 2.87 (1H, m), 3.12 (2H, m), 3.30 (2H, m), 3.60 (2H, m),
 5.25 (2H, brs), 6.07 (1H, t), 6.67-7.04 (3H, m), 7.16-7.38 (4H, m), 7.58 (1H, m), 7.96 (1H, m), 8.52 (1H, m). COOH signal was not observed.

MS m/z: 533 (M+1)

Example 157 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 51, but replacing the product of example 50 with the product of example 156.

¹H-NMR (CD₃OD) δ: 1.66-1.98 (4H, m), 2.40-2.73 (5H, m), 2.82-2.94 (2H, m), 3.22 (2H, m), 3.84 (2H, dd), 4.01 (2H, dd), 5.23 (2H, brs), 6.13 (1H, t), 6.64-6.98 (3H, m), 7.13-7.34 (4H, m), 7.45 (1H, m), 7.77 (1H, m), 8.47 (1H, m). OH signal was not observed.

MS m/z: 491 (M+1)

Example 160 - 1-[3-(8-Bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine

The titled compound was prepared by following the procedure of example 65, but replacing the product of example 45, step 2 with the product of example 54, step 1.

¹H-NMR (CDCl₃) δ: 1.50-1.86 (4H, m), 1.98 (2H, m), 2.26-2.60 (5H, m), 2.88 (2H, m), 5.30 (2H, brs), 6.09 (1H, t), 6.96-7.36 (8H, m), 7.57 (1H, dd), 8.51 (1H, dd).

MS m/z: 509, 511 (M+1)

Example 158 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl-1-methylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 138, but replacing the product of example 44 with the product of example 151.

¹H-NMR (CDCl₃) δ: 1.28 (3H, t), 1.56 (6H, s), 1.56-1.85 (4H, m), 1.97 (2H, dt), 2.28-2.55 (5H, m), 2.93 (2H, m), 4.24 (2H, q),

Example 161 - 1-[3-(8-Carboxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-

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(4-chlorophenyl)piperidine

To a solution of 1-[3-(8-Bromo-5,11-

dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidine (Example 161) (130 mg) in

5 THF(1.0 mL) was added 1.6M n-butyllithium hexane solution (0.17 mL) at -78°C. After stirring 10 minutes at the same

temperature, CO₂ (dry-ice) was added to the mixture. After being warmed to ambient temperature, the mixture was stirred for 30 minutes at the same temperature. The

10 mixture was concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluted with dichloromethane -methanol (5:1) to give the titled

compound

¹H-NMR (CD₃OD) δ: 1.55-1.95(4H,m), 2.17(2H,dt), 2.32-

15 2.78(5H,m), 3.00(2H,m), 5.30(2H,brs), 6.19(1H,t), 7.08-7.54(8H,m), 7.76(1H,dd), 8.45(1H,dd). COOH signal was not observed (50 mg).

MS m/z: 475(M+1)

Example 162 - 1-[3-(7-Bromo-5,11-

20 dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing

5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with

5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one.

25 with 8-bromo-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.60-1.71(3H,m), 1.98-2.09(2H,m), 2.34-2.69(8H,m), 5.32(2H,brs), 6.13(1H,t), 6.73(1H,d), 7.22-7.44(7H,m), 7.57(1H,dd), 8.52(1H,dd).

MS m/z: 525, 527(M+1)

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To a solution of 1-[3-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with

5,11-dihydro-7-ethyl[1]benzoxepino[2,3-b]pyridin-5-one.

10 1H-NMR (CDCl₃) δ: 1.23(3H,t), 1.52(1H,brs),

1.66-1.71(2H,m), 1.98-2.06(2H,m), 2.35-2.70(1H,m),

5.31(2H,brs), 6.09(1H,t), 6.79(1H,d), 7.01(1H,dd), 7.11(1H,d), 7.25-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).

15 MS m/z: 475(M+1)

Example 164 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing

20 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with

5,11-dihydro-8-vinyl[1]benzoxepino[2,3-b]pyridin-5-one.

1H-NMR (CDCl₃) δ: 1.66-1.71(3H,m), 2.00-2.10(2H,m), 2.36-2.70(8H,m), 5.22(2H,d), 5.34(2H,brs), 5.70(1H,d),

25 6.11(1H,t), 6.61(1H,dd), 6.89(1H,d), 6.99(1H,dd), 7.24-7.44(6H,m), 7.58(1H,dd), 8.49(1H,dd).

MS m/z: 473(M+1)

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Example 165 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-8-ethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

A mixture of the product of example 164 (100 mg) and Pd-C (20 mg) in ethanol (2 ml) stirred under a hydrogen balloon at room temperature for 1 hour. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by preparative thin layer chromatography eluting with chloroform-methanol (15:1) to give the titled compound (50 mg).

¹H-NMR (CDCl₃) δ: 1.22 (3H, t), 1.55-1.77 (3H, m), 2.00-2.13 (2H, m), 2.33-2.74 (10H, m), 5.32 (2H, brs), 6.07 (1H, t), 6.70 (1H, d), 6.78 (1H, dd), 7.19-7.44 (6H, m), 7.57 (1H, dd), 8.49 (1H, dd).

MS m/z: 475 (M+1)

Example 167 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzoxepino[4,3-c]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzoxepino[4,3-c]pyridin-5-one.

¹H-NMR (CDCl₃) δ: 1.67-1.71 (2H, m), 2.16 (1H, s), 2.40-2.69 (8H, m), 5.16 (2H, brs), 6.14 (1H, t), 6.80 (1H, dd), 6.91-6.97 (1H, m), 7.13-7.19 (1H, m), 7.26-7.44 (6H, m), 7.50-8.54 (2H, m). MS m/z: 447 (M+1)

Example 166 - 4-(4-Chlorophenyl)-1-[3-(5,11-dimethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzoxepino[4,3-d]pyrimidin-5-one.

¹H-NMR (CDCl₃) δ: 1.68-1.72 (2H, m), 1.90 (1H, brs), 2.06-2.19 (2H, m), 2.41-2.78 (8H, m), 5.20 (2H, s), 6.12 (1H, t), 7.14-7.45 (8H, m), 8.72 (1H, s), 8.97 (1H, s).

MS m/z: 448 (M+1)

Example 168 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro[1]benzoxepino[4,3-d]pyrimidin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 5,11-dihydro[1]benzoxepino[4,3-d]pyrimidin-5-one.

¹H-NMR (CDCl₃) δ: 1.68-1.72 (2H, m), 1.90 (1H, brs), 2.06-2.19 (2H, m), 2.41-2.78 (8H, m), 5.20 (2H, s), 6.12 (1H, t), 7.14-7.45 (8H, m), 8.72 (1H, s), 8.97 (1H, s).

MS m/z: 448 (M+1)

Example 169 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-trifluoromethanesulfonyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of example 44 (1.0 g) in pyridine (10 ml) was added trifluoromethanesulfonic acid

MS m/z: 477 (M+1)

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anhydride (0.55 ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. Water and diethyl ether were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (10:1) to give the titled compound {1.1 g}.

¹H-NMR (CDCl₃) δ: 1.56(1H, brs), 1.66-1.71(2H, m), 1.97-2.09(2H, m), 2.35-2.69(8H, m), 5.35(2H, brs) 6.15(1H, t), 6.88(1H, d), 7.05(1H, dd), 7.21-7.44(6H, m), 7.60(1H, dd), 8.54(1H, dd).
MS m/z: 595(M+1)

Example 170 - 1-[3-(7-(2-t-Butoxycarboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol
(4-chlorophenyl)piperidin-4-ol

A mixture of the product of example 169 (1.7 g), t-butyl acrylate (0.85 ml), triethylamine (2.5 ml), 1,1'-bis(diphenylphosphino)ferrocene (250 mg) and palladium(II) diacetate (33 mg) in dimethylformamide (3 ml) under argon at 90°C for 24 hours. Water ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (30:1) to give the titled compound (0.19 ml).

allyltributyltin (0.19 ml), dichlorobis(triphenylphosphine)palladium(II) (30 mg), lithium chloride (76 mg), in dimethylformamide (3 ml) under argon at 120°C for 2 hours. Aqueous ammonium fluoride solution and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (180 mg).

¹H-NMR (CDCl₃) δ: 1.62-1.72(3H, m), 2.03-2.11(2H, m), 2.39-2.73(8H, m), 3.31(2H, d), 5.04-5.11(2H, m), 5.29(2H, brs), 5.87-6.02(1H, m), 6.06(1H, t), 6.77(1H, d), 6.99(1H, dd), 7.10(1H, d), 7.23-7.43(5H, m), 7.57(1H, dd), 8.40(1H, dd).

Example 171 - 1-[3-(7-(2-t-Butoxycarboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

A mixture of the product of example 169 (1.7 g), t-butyl acrylate (0.85 ml), triethylamine (2.5 ml), 1,1'-bis(diphenylphosphino)ferrocene (250 mg) and palladium(II) diacetate (33 mg) in dimethylformamide (3 ml) under argon at 90°C for 24 hours. Water ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (30:1) to give the titled compound (0.19 ml).

allyltributyltin (0.19 ml), dichlorobis(triphenylphosphine)palladium(II) (30 mg), lithium chloride (76 mg), in dimethylformamide (3 ml) under argon at 120°C for 2 hours. Aqueous ammonium fluoride solution and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (180 mg).

¹H-NMR (CDCl₃) δ: 1.45(9H, s), 1.63-1.71(3H, m), 1.98-2.10(2H, m), 2.35-2.72(8H, m), 5.35(2H, brs), 6.15(1H, t), 6.26(1H, d), 6.83(1H, d), 7.22-7.44(7H, m), 7.53(1H, d), 7.58(1H, dd), 8.52(1H, dd).

Example 172 - 1-[3-(7-(2-Carboxy)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

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The product of example 171 (330 mg) was dissolved with 4N hydrochloric acid 1,4-dioxane solution (4 mL), and stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure. Water was added to the residue, and neutralized with sodium hydroxide solution. The precipitation was filtered to give the titled compound (190 mg).

¹H-NMR (DMSO-d₆) δ: 1.45-1.52(2H,m), 1.72-1.84(2H,m), 2.25-2.58(8H,m), 5.25(2H,brs), 6.28(1H,t), 6.43(1H,d), 6.82(1H,d), 7.34-7.60(8H,m), 7.75(1H,dd), 8.52(1H,dd).

Example 173 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

propargyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with propargyl chloride.

¹H-NMR (CDCl₃) δ: 1.66-1.71(2H,m), 1.79(1H,brs), 1.99-2.10(2H,m), 2.35-2.71(9H,m), 4.66(2H,d), 5.28(2H,brs), 6.10(1H,t), 6.80-6.93(3H,m), 7.24-7.46(5H,m), 7.59(1H,dd), 8.48(1H,dd). MS m/z: 501(M+1)

Example 174 - 4-(4-Chlorophenyl)-1-[3-(7-cyclopentoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with cyclopentyl bromide.

¹H-NMR (CDCl₃) δ: 1.54-2.18(13H,m), 2.41-2.72(8H,m), 4.66-4.73(1H,m), 5.27(2H,brs), 6.08(1H,t), 6.70-6.87(3H,m), 7.23-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).

5 MS m/z: 531(M+1)

Example 175 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-methoxyethyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 2-methoxyethyl chloride.

¹H-NMR (CDCl₃) δ: 1.66-1.75(3H,m), 2.00-2.11(2H,m), 2.36-2.71(8H,m), 3.45(3H,s), 3.71-3.75(2H,m), 4.07-4.11(2H,m), 5.27(2H,brs), 6.09(1H,t), 6.75-6.91(3H,m), 7.23-7.44(5H,m), 7.57(1H,dd), 8.48(1H,dd). MS m/z: 521(M+1)

Example 176 - 4-(4-Chlorophenyl)-1-[3-(7-(1-dimethylaminocarbonyl-1-methyl ethyloxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 139.

¹H-NMR (CDCl₃) δ: 1.59(6H,s), 1.67-1.72(2H,m), 1.99-2.09(2H,m), 2.36-2.70(9H,m), 2.96(3H,s), 3.21(3H,s), 5.25(2H,brs), 6.02(1H,t), 6.60-6.77(3H,m), 7.24-7.44(5H,m), 7.58(1H,dd), 8.44(1H,dd).

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MS m/z: 576 (M+1)

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 2-bromocyclobutanecarboxylate.

Example 177 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonylethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 2-bromopropionate.

1H-NMR (CDCl_3) δ : 1.25 (3H, t), 1.59 (3H, d), 1.65-1.70 (2H, m), 1.98-2.08 (2H, m), 2.35-2.68 (8H, m), 2.80 (1H, brs), 4.21 (2H, q), 4.21 (2H, q), 4.68 (1H, q), 5.24 (2H, brs), 6.07 (1H, t), 6.68-6.79 (2H, m), 6.88 (1H, d), 7.22-7.44 (5H, m), 7.56 (1H, dd), 8.40 (1H, dd).

Example 178 - 1-[3-(7-(1-Carboxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 177.

1H-NMR (DMSO-d_6) δ : 1.46 (3H, d), 1.58-1.63 (2H, m), 1.98-2.06 (2H, m), 2.41-2.45 (2H, m), 2.72-2.86 (6H, m), 4.74 (1H, q), 5.18 (2H, brs), 6.11 (1H, t), 6.73 (2H, s), 6.84 (1H, s), 7.36-7.47 (5H, m), 7.73 (1H, dd), 8.50 (1H, dd). MS m/z: 535 (M+1)

Example 181 - 1-[3-(7-Carbamoylmethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine hydrochloride with ammonium hydroxide.

Example 179 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarbonyl)cyclobutoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

1H-NMR (CDCl_3) δ : 1.66-1.71 (2H, m), 1.98-2.09 (2H, m), 2.21 (1H, brs), 2.38-2.70 (8H, m), 4.45 (2H, s), 5.28 (2H, brs), 6.09 (1H, t), 6.11 (1H, brs), 6.58 (1H, brs), 6.74-6.85 (3H, m), 7.24-7.44 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).

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MS m/z: 520 (M+1)

Example 182 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methyloxymethyl)propyl]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine hydrochloride with methylamine.

¹H-NMR (CDCl₃) δ: 1.67-1.72 (2H, m), 1.99-2.10 (2H, m), 2.36-2.70 (9H, m), 2.89 (3H, d), 4.45 (2H, s), 5.28 (2H, brs), 6.08 (1H, t), 6.66 (1H, brs), 6.73-6.84 (3H, m), 7.25-7.45 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).

MS m/z: 534 (M+1)

Example 183 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(3-cj[1]benzoxepipin-5-ylidene)propyl]-4-

The titled compound was prepared by following the procedure of example 45, step 3, but replacing (4-hydroxyphenyl)piperidine with

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

¹H-NMR (CDCl₃) δ: 1.52-1.88 (4H, m), 2.01 (2H, dt), 2.28-2.60 (5H, m), 2.93 (2H, m), 3.79 (3H, s), 5.28 (2H, brs), 6.08 (1H, t), 6.68-6.88 (3H, m), 7.05-7.36 (5H, m), 7.58 (1H, dd), 8.50 (1H, dd).

MS m/z: 461 (M+1)

Example 184 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-

Example 186 - 4-(7-Chloro-1,2-benzisoxazol-3-yl)-1-[3-(5,11-dihydro-7-

3-cj[1]benzoxepipin-5-ylidene)propyl]-4-(2-hydroxyphenyl)piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(2-hydroxyphenyl)piperidine.

¹H-NMR (CDCl₃) δ: 1.78-1.92 (4H, m), 2.12-2.25 (2H, m), 2.32-2.70 (4H, m), 2.80-2.97 (1H, m), 3.01-3.15 (2H, m), 3.77 (3H, s), 3.78 (1H, brs), 5.28 (2H, brs), 6.03 (1H, t), 6.74-6.86 (4H, m), 7.05 (1H, dd), 7.11 (1H, dd), 7.23-7.28 (2H, m), 7.56 (1H, dd), 8.48 (1H, dd), OH signal was not observed.

MS m/z: 443 (M+1)

Example 185 - 4-(7-Chloro-1,2-benzisoxazol-3-yl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

4-(7-chloro-1,2-benzisoxazol-3-yl) piperidine. This piperidine was prepared by the same method described in J. Med. Chem. 28:761-769 (1985).

¹H-NMR (CDCl₃) δ: 1.94-2.20 (6H, m), 2.30-2.60 (4H, m), 2.86-3.14 (3H, m), 3.79 (3H, s), 5.29 (2H, brs), 6.10 (1H, t), 6.70-6.88 (3H, m), 7.22 (1H, t), 7.27 (1H, dd), 7.50 (1H, dd), 7.57-7.68 (2H, m), 8.49 (1H, dd).

MS m/z: 461 (M+1)

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The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloroindol-3-yl)piperidine. This piperidine was prepared by the same method described in *J. Med. Chem.* 36:4006-4014 (1993) and following hydrogenation described in Example 58, step 3.

¹H-NMR (CDCl₃) δ: 1.66-1.88 (2H,m), 1.92-2.22 (4H,m), 2.32-2.63 (4H,m), 2.78 (1H,m), 2.97 (2H,m), 3.79 (3H,s), 5.29 (2H,brs), 6.09 (1H,t), 6.70-6.87 (3H,m), .6.97-7.07 (2H,m), 7.12-7.30 (2H,m), 7.52 (1H,m), 7.59 (1H,dd), 8.45 (1H,brs), 8.50 (1H,dd).

Example 187 - 4-Azido-4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine (15): Fig. 8b

To a cold (0°C) solution of 1 (3.0 g, 14 mmol) in anhydrous dioxane (15 mL) under an inert atmosphere was added NaN₃ (1.0 g, 15.4 mmol) followed by the slow dropwise addition of and BF₃•OEt₂ (4.4 mL, 35 mmol). The reaction was stirred at 0 °C for 3 hrs and was quenched at 0 °C by the slow careful addition of saturated aqueous NaHCO₃ to basicity. The organic layer was separated and dried over Na₂SO₄. The reaction mixture was purified via silica gel flash chromatography eluting a 2 g 1:3 mixture of azidopiperidine 2 and olefin 3 with 2% MeOH/CH₂Cl₂. The mixture was taken directly on to the next reaction.

Step 2

5 prepared by the same method described in *J. Med. Chem.* 36:4006-4014 (1993) and following hydrogenation described in Example 58, step 3.

¹H-NMR (CDCl₃) δ: 1.88 (2H,m), 2.55-2.85 (4H,m), 3.00-3.30 (6H,m), 3.75 (3H,s), 5.19 (2H,brs), 5.97 (1H,t), 6.68-6.65 (3H,m), 7.20-7.46 (5H,m), 7.63 (1H,dd), 8.35 (1H,dd), 10 MS m/z: 477 (M+1-N₂+H₂)

The titled compound was prepared by then following the procedure of example 45, step 3, with the above reaction mixture (thereby replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-azido-4-(4-chlorophenyl)piperidine), but limiting the amount of bromide to 0.25 equivalents.

¹H-NMR (CDCl₃) δ: 1.88 (2H,m), 2.55-2.85 (4H,m), 3.00-3.30 (6H,m), 3.75 (3H,s), 5.19 (2H,brs), 5.97 (1H,t), 6.68-6.65 (3H,m), 7.20-7.46 (5H,m), 7.63 (1H,dd), 8.35 (1H,dd), 10 MS m/z: 477 (M+1-N₂+H₂)

Example 188 - Methyl 1-[3-(5,11-dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidin-4-carboxylate

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with methyl 4-phenylpiperidin-4-carboxylate.

¹H-NMR (CDCl₃) δ: 1.82-2.15 (4H,m), 2.28-2.60 (6H,m), 2.78-2.82 (2H,m), 3.62 (3H,s), 3.68 (3H,s), 5.26 (2H,brs), 5.95 (0.1H,t, E isomer), 6.05 (0.9H,t, Z isomer), 6.82-6.70 (3H,m), 7.33-7.22 (6H,m), 7.65 (0.1H,dd, Z isomer), 7.55 (0.9H,dd, Z isomer), 8.39 (0.1H, E isomer), 8.48 (0.9H,dd, Z isomer).
MS m/z: 485 (M+1)

25 Example 189 - 1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-phenylpiperidin-4-carboxylic acid

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The titled compound was prepared by following the procedure of example 133, but replacing product of example 48 with product of example 188.

¹H-NMR (CD₃OD) δ: 2.16-2.23 (2H, m), 2.69-2.91 (4H, m), 3.00-

5 3.16 (2H, m), 3.37-3.25 (2H, m), 3.68-3.73 (2H, m), 3.76 (3H, s),

5.34 (2H, brs), 6.24 (1H, t), 6.70-7.04 (3H, m), 7.26-

7.55 (5H, m), 7.79-7.89 (1H, m), 8.21-8.34 (1H, m), 8.56-

8.62 (0.1H, m), 8.63-8.77 (0.9H, m),

MS m/z: 471 (M+1)

10 Example 190 - 1-(2-Chlorophenylsulfonyl)-4-[3-(5,11-

Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl)piperazine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing

15 4-(4-chlorophenyl)-4-hydroxypiperidine with

1-(2-chlorophenylsulfonyl)piperazine.

¹H-NMR (CDCl₃) δ: 2.20-2.58 (8H, m), 3.12-3.38 (4H, m),

3.76 (3H, s), 5.22 (2H, brs), 6.03 (1H, t), 6.64-6.90 (3H, m),

7.23 (1H, dd), 7.32-7.60 (4H, m), 8.01 (1H, dd), 8.48 (1H, dd).

20 MS m/z: 526 (M+1)

Example 193 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine

The titled compound was prepared by following the

20 procedure of example 44, step 2, but replacing

4-(4-chlorophenyl)-4-hydroxypiperidine with
4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.

The titled compound was prepared by following the

25 procedure of example 45, step 3, but replacing
4-(4-chlorophenyl)-4-hydroxypiperidine with

1-(3-chlorophenylsulfonyl)piperazine.

Example 194 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

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methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine.

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine.

¹H-NMR (CDCl₃) δ: 2.37-2.72 (8H, m), 3.06 (2H, m), 3.78 (3H, s), 5.27 (2H, brs), 5.99 (1H, m), 6.10 (1H, t), 6.72-6.90 (3H, m), 7.20-7.44 (5H, m), 7.60 (1H, dd), 8.50 (1H, dd).

MS m/z: 459 (M+1)

Example 195 - 4-(7-Chloroindol-3-yl)-1-[3-(5,11-dihydro-7-(2-methoxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-1,2,3,6-tetrahydropyridine.

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(7-chloroindol-3-yl)-1,2,3,6-tetrahydropyridine. This piperidine was prepared by the same method described in J. Med. Chem., 36:4006-4014 (1993).

¹H-NMR (CDCl₃) δ: 2.37-2.76 (8H, m), 3.14 (2H, m), 3.78 (3H, s),

5.29 (2H, brs), 6.02-6.23 (2H, m), 6.67-6.90 (3H, m), 7.05 (1H, dd), 7.12-7.33 (3H, m), 7.60 (1H, dd), 7.77 (1H, m), 8.50 (1H, dd), 9.06 (1H, br s).

20 Example 196 -

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[isobenzofuran-1(3H),4'-piperidine].

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-dimethylaminocarbonyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol.

The titled compound was prepared by following the procedure of example 134, but replacing the product of example 133 with the product of example 118.

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¹H-NMR (CDCl₃) δ: 1.65-1.70(2H,m), 1.99-2.09(3H,m), 2.32-2.69(8H,m), 2.17(3H,s), 5.35(2H,brs), 6.15(1H,t), 6.82(1H,d), 7.19(1H,dd), 7.28-7.46(6H,m), 7.58(1H,dd), 8.49(1H,dd).

5 Example 199 -

4-(4-Chlorophenyl)-1-[3-(7-(2-(1-hydroxy-2-methyl)propyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol.

To a solution of product of example 138 (500 mg) in methanol (5 mL) was added sodium borohydride (330 mg), and the mixture was heated to reflux for 1 hour. The mixture was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The residue was purified by

¹H-NMR (CDCl₃) δ: 1.34(6H,s), 1.58(1H,brs), 1.66-1.71(2H,m), 1.99-2.10(2H,m), 2.25(1H,brs), 2.36-2.71(8H,m), 3.77(2H,s), 5.28(2H,brs), 6.09(1H,t), 6.74-6.86(3H,m), 7.24-7.44(5H,m), 7.57(1H,dd), 8.49(1H,dd).

MS m/z: 535(M+1)

with chloroform:methanol (10:1) to give the titled compound (440 mg).

20 ¹H-NMR (CDCl₃) δ: 1.26(6H,s), 1.66-1.70(2H,m), 1.79(1H,brs), 2.00-2.08(2H,m), 2.37-2.70(9H,m),

3.58(2H,s), 5.30(2H,brs), 6.05(1H,t), 6.75-6.84(2H,m),

6.91(1H,d), 7.26-7.44(5H,m), 7.58(1H,dd), 8.49(1H,dd).

MS m/z: 535(M+1)

Example 203

4-(4-Chlorophenyl)-1-[3-(7-(2-ethoxy)ethoxy)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 2-ethoxyethyl bromide.

25 Example 200 -

4-(4-Chlorophenyl)-1-[3-(7-(1-(2-methyl-2-hydroxy)propyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

¹H-NMR (CDCl₃) δ: 1.24(3H,t), 1.66-1.75(3H,m), 2.00-2.11(2H,m), 2.36-2.71(8H,m), 3.59(2H,q), 3.71-3.75(2H,m), 4.07-4.11(2H,m), 5.27(2H,brs), 6.09(1H,t), 6.75-6.91(3H,m), 7.23-7.44(5H,m), 7.57(1H,dd), 8.48(1H,dd).

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MS m/z: 535 (M+1)**Example 205**
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-(2,3-dihydroxy)propoxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with glycidol.

¹H-NMR (CDCl₃) δ: 1.66-1.75 (2H, m), 2.00-2.11 (2H, m), 2.36-2.71 (8H, m), 3.62-3.76 (2H, m), 3.94-4.02 (4H, m), 4.21 (2H, brs), 5.27 (2H, brs), 6.09 (1H, t), 6.76-6.86 (3H, m), 7.23-7.44 (5H, m), 7.57 (1H, dd), 8.48 (1H, dd).

MS m/z: 537 (M+1)

Example 211
4-(4-Chlorophenyl)-1-[3-(7-(1-Carbamoyl-1-methyl)ethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing dimethylamine with methylamine.

¹H-NMR (CDCl₃) δ: 1.47 (6H, s), 1.67-1.72 (2H, m), 1.96-2.09 (2H, m), 2.20 (1H, brs), 2.36-2.70 (8H, m), 2.87 (3H, d), 5.29 (2H, brs), 6.04 (1H, t), 6.72-6.86 (4H, m), 7.27-7.44 (5H, m), 7.58 (1H, dd), 8.47 (1H, dd).

MS m/z: 562 (M+1)

Example 215**Example 211**
4-(4-Chlorophenyl)-1-[3-(7-(2-dimethylaminocarbonyl)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 176, but replacing dimethylamine with ammonium hydroxide.

The titled compound was prepared by following the procedure of example 176, but replacing dimethylamine with ammonium hydroxide.

¹H-NMR (CDCl₃) δ: 1.50 (6H, s), 1.67-1.72 (2H, m), 1.96-2.09 (3H, m), 2.36-2.70 (8H, m), 5.30 (2H, brs), 5.70 (1H, brs), 6.05 (1H, t), 6.75-6.90 (4H, m), 7.25-7.44 (5H, m), 7.58 (1H, dd), 8.49 (1H, dd).

MS m/z: 548 (M+1)

Example 218

1-[3-(7-(2-Carbamoyl)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

Example 212

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The titled compound was prepared by following the procedure of example 181, but replacing the product of, example 133 with the product of example 123.

¹H-NMR (CDCl₃) δ: 1.65-1.90 (3H, m), 2.10-2.22 (2H, m),
 5 2.40-2.80 (10H, m), 2.91 (2H, t), 5.31-5.46 (4H, m), 6.11 (1H, t),
 6.78 (1H, d), 7.01 (1H, dd), 7.16 (1H, d), 7.28-7.46 (5H, m),
 7.57 (1H, dd), 8.49 (1H, dd).
 MS m/z: 518 (M+1)

Example 234 - 1-[3-(5,11-Dihydro-7-

10 methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(indol-3-yl)-piperidine

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

15 4-(indol-3-yl)-piperidine. This piperidine was prepared by the same method described in J. Med. Chem. 36:4006-4014 (1993) and follow hydrogenation described in Example 58, step 3.

¹H-NMR (CDCl₃) δ: 1.65-1.93 (2H, m), 1.94-2.28 (4H, m), 2.34-

20 2.70 (4H, m), 2.81 (1H, m), 2.96 (2H, m), 3.78 (3H, s),
 5.28 (2H, brs), 6.09 (1H, t), 6.70-7.42 (8H, m), 7.53-
 7.72 (2H, m), 8.28 (1H, brs), 8.49 (1H, m).

Example 235 - 1-[3-(5,11-Dihydro-7-

methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-

25 (indol-3-yl)-1,2,3,6-tetrahydropyridine.

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with

30 signal was not observed.

4-(indol-3-yl)-1,2,3,6-tetrahydropyridine. This piperidine was prepared by the same method described in J. Med. Chem. 36:4006-4014 (1993).

¹H-NMR (CDCl₃) δ: 2.35-2.77 (8H, m), 3.06-3.26 (2H, m),
 5 3.78 (3H, s), 5.29 (2H, brs), 6.05-6.22 (2H, m), 6.70-
 6.88 (3H, m), 7.07-7.38 (5H, m), 7.60 (1H, dd), 7.87 (1H, m),
 8.42 (1H, brs), 8.50 (1H, m).

Example 236 - 4-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-(3-

(ethoxycarbonyl)propyloxy[1]benzoxepino[2,3-b]pyridin-5-10
 ylidine)propyl]piperidine

The titled compound was prepared by following the procedure of example 153, but replacing ethyl bromoacetate with ethyl 4-bromobutyrate.

¹H-NMR (CDCl₃) δ: 1.26 (3H, t), 1.56-1.85 (4H, m), 2.01 (2H, dt),
 15 2.09 (2H, quint), 2.30-2.60 (7H, m), 2.93 (2H, m), 3.98 (2H, t),
 4.15 (2H, q), 5.28 (2H, brs), 6.07 (1H, t), 6.68-6.86 (3H, m),
 7.07-7.33 (5H, m), 7.58 (1H, dd), 8.50 (1H, dd).
 MS m/z: 561 (M+1)

Example 237 - 1-[3-(7-(3-Carboxypropyl)oxy-5,11-dihydro-[1]benzoxepino[2,3-b]pyridin-5-ylidine)propyl]-4-(4-chlorophenyl)-piperidine

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 236.

¹H-NMR (CD₃OD) δ: 1.92-2.20 (6H, m), 2.48 (2H, t), 2.70-
 3.02 (3H, m), 3.06-3.45 (4H, m), 3.66 (2H, m), 4.01 (2H, t),
 5.48 (2H, brs), 6.36 (1H, t), 6.85 (2H, s), 7.00 (1H, s), 7.20-
 7.40 (4H, m), 8.11 (1H, dd), 8.64 (1H, d), 8.81 (1H, d). COOH

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MS m/z: 533 (M+1)

Example 242

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-hydroxy-1-methyl)ethyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 200, but replacing the product of example 48 with the product of example 273.

¹H-NMR (CDCl₃) δ: 1.58 (6H, s), 1.65-1.70 (3H, m), 1.93-2.21 (2H, m), 2.28-2.73 (8H, m), 5.32 (2H, brs), 6.13 (1H, t), 6.82 (1H, d), 7.20-7.50 (7H, m), 7.59 (1H, dd), 8.50 (1H, dd).

MS m/z: 505 (M+1)

Example 243

1-[3-(7-(1-Carboxy-1-methyl)ethyl)-5, 11-dihydro[1]benzoxepino [2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

To a solution of Example 363, step 2 (2.4 g) in toluene (30 mL) was added DIBAL (1 mol/L toluene solution, 9.2 mL)

at -78°C, and the mixture stirred at 0°C for 1 hour, and at room temperature for 30 minutes. The reaction mixture

was added saturated aqueous ammonium chloride. 1 N aqueous hydrochloric acid, saturated sodium chloride and ethyl acetate were added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl

acetate-hexane (1:4) to give 5-(3-bromopropylidene)-5, 11-dihydro-7-(1-hydroxy-1-methyl)ethyl[1]benzoxepino[2m3ob]pyridine (2.0 g).

¹H-NMR (CDCl₃) δ: 1.45 (H, s), 2.75 (2H, q), 3.47 (1H, t), 5.33 (2H, brs), 6.04 (1H, t), 6.87 (1H, d), 7.09-7.14 (2H, m), 7.30 (1H, dd), 7.57 (1H, dd), 8.53 (1H, dd), 9.46 (1H, s),

Step 2

5-(3-bromopropylidene)-7-(1-carboxy-1-methyl)ethyl-5, 11-dihydro[1]benzoxepino [2,3-b]pyridine was prepared by following the procedure of Example 382, step 2, but replacing the product of Example 382, step 1 with the product of step 1 above.

Step 3

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 2.

¹H-NMR (DMSO-d₆) δ: 1.46 (6H, s), 1.63-1.84 (2H, m), 2.17-2.37 (4H, m), 2.37-2.53 (4H, m), 3.20-3.43 (2H, m), 4.83 (1H, s), 5.23 (2H, brs), 6.13 (1H, t), 6.76 (1H, d), 7.16 (1H, dd), 7.25 (1H, d), 7.35 (2H, d), 7.42-7.48 (3H, m), 7.76 (1H, dd), 8.50 (1H, dd). MS m/z: 533 (M+1)

Example 248 - 1-[3-(5,11-Dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-6-methylspiro[4H-3,1-benzoxazine-4,4'-piperidine]-2(1H)-one

The titled compound was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 6-methylspiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

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¹H-NMR (CDCl₃) δ: 1.99-2.06 (2H, m), 2.29 (3H, s), 2.32-2.69 (10H, m), 3.77 (3H, s), 5.27 (2H, brs), 6.08 (1H, t), 6.69-6.83 (4H, m), 6.94 (1H, s), 7.02 (1H, d), 7.25 (1H, dd), 7.55 (1H, dd), 8.48 (1H, dd), 8.56 (1H, s).

5 MS m/z: 498 (M+1)

Example 249 - 5-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4,6-dioxazacane.

5-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4,6-diazacyclooctylamine

Step 1

5-(3-(N,N'-Bis(2-hydroxyethyl)amino)propylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with diethanolamine.

¹H-NMR (CD₃OD) δ: 2.46 (2H, m), 2.84 (4H, t), 2.98 (2H, m), 3.67 (4H, t), 3.75 (3H, s), 5.20 (2H, brs), 6.16 (1H, t), 6.68-6.80 (2H, m), 6.87 (1H, d), 7.46 (1H, dd), 7.81 (1H, dd), 8.45 (1H, dd).

20 Step 2

To a cold (0°C) stirred solution of 4-oxohomopiperidine•HCl (0.6 g, 4.05 mmol), K₂CO₃ (0.615 g, 4.46 mmol) in anhydrous THF (10 mL) will be ethyl chloroformate (0.44 mL, 4.05 mmol) dropwise. The reaction was warmed to RT for 2 hrs then quenched with H₂O, extracted with EtOAc, and the organic layer dried over Na₂SO₄. Pure 1-ethylcarbonyl-4-oxohomopiperidine will be isolated via silica gel flash chromatography

20 Step 1

and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel chromatography eluting with dichloromethane-methanol (20:1) to give the titled compound (40mg). ¹H-NMR (CDCl₃) δ: 2.35 (2H, m), 2.64-2.94 (6H, m), 3.52-3.68 (2H, m), 3.78 (3H, s), 3.72-3.90 (2H, m), 5.27 (2H, brs), 5.66 (1H, s), 6.08 (1H, t), 6.68-6.88 (3H, m), 7.18-7.46 (5H, m), 7.58 (1H, dd), 8.50 (1H, dd).

10 Example 252

Step 1

To a cold (0°C) stirred solution of 4-oxohomopiperidine•HCl (0.6 g, 4.05 mmol), K₂CO₃ (0.615 g, 4.46 mmol) in anhydrous THF (10 mL) will be ethyl chloroformate (0.44 mL, 4.05 mmol) dropwise. The reaction was warmed to RT for 2 hrs then quenched with H₂O, extracted with EtOAc, and the organic layer dried over Na₂SO₄. Pure 1-ethylcarbonyl-4-oxohomopiperidine will be isolated via silica gel flash chromatography

20 To a cold (0°C) stirred solution of 1-ethylcarbonyl-4-oxohomopiperidine (1.42 g, 6.07 mmol) in anhydrous THF (50 mL) under argon can be added dropwise 1.0 mM 4-chlorophenylmagnesium bromide in diethyl ether (10 mL, 10mmol). The reaction can be warmed to RT for 2 hrs then quenched with saturated aqueous NH₄Cl 95 mL. The reaction mixture can then be extracted with EtOAc (2 X 50 mL), the organic layers combined and dried over Na₂SO₄. Pure 1-ethoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopiperidine

Step 2
To a mixture of product of step 1 (78mg) and 4-chlorobenzaldehyde dimethyl acetal (0.1ml) in 1,2-dichloroethane (60ml) was added p-toluenesulfonic acid monohydrate (5mg) at room temperature, and the mixture was stirred at reflux for 12 hours. Dichloromethane and saturated aqueous sodium bicarbonate was added to the cooled reaction mixture, the organic layer was separated

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(2.1 g, 96%) can be isolated via silica gel flash chromatography eluting with 50% EtOAc/hexane.

4-(4-chlorophenyl)-4-hydroxyhomopiperidine can be prepared by reacting 1-ethoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopeperidine with a nucleophilic hydroxide equivalent such as LiOH in a solvent such as THF, methanol or ethanol. Removal of the solvent can afford 4-(4-chlorophenyl)-4-hydroxyhomopeperidine.

Step 4

The compound was prepared by following the procedure for Example 44, but replacing 4-(4-chlorophenyl)-4-

hydroxypeperidine with 4-(4-chlorophenyl)-4-hydroxyhomopeperidine.

Examples 253 and 254

Step 1

To a stirred solution of 4-oxohomopiperidine•HCl (1.2 g, 8.05 mmol), NaOH (0.68 g, 16.9 mmol) in t-BuOH/H₂O (1:1, 10 mL) was added t-butylidicarbonate (1.93 mL, 8.9 mmol) dropwise. The reaction was stirred at RT overnight, extracted with EtOAc (2 X 10 mL) and the organic layer separated.

The organic layer was dried over Na₂SO₄ and concentrated under vacuo. Pure 1-t-butoxycarbonyl-4-oxohomopiperidine (1.42 g, 84%) was isolated via silica gel flash

chromatography eluting with 50% EtOAc/hexane. ¹H NMR CDCl₃, CDCl₃, 4.4 (9H, s), 1.72-1.84 (2H, m), 2.60-2.65 (4H, m), 3.55-3.61 (4H, m).

Step 2

To a cold (0°C) stirred solution of 1-t-butoxycarbonyl-4-oxohomopiperidine (1.42 g, 6.07 mmol) in anhydrous THF (50

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mL) under argon was added dropwise 1.0 M 4-chlorophenylmagnesium bromide in diethyl ether (10 mL, 10 mmol). The reaction was warmed to RT for 2 hrs then

quenched with sat'd aqueous NH₄Cl (5 mL). The reaction mixture was extracted with EtOAc (2 X 50 mL), the organic layers combined and dried over Na₂SO₄. Pure 1-t-butoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopiperidine (2.1 g, 96%) was isolated via silica gel flash chromatography eluting with 50% EtOAc/hexane. ¹H NMR CDCl₃, 1.43 (9H, s), 1.61-2.22 (6H, m), 3.21-3.031 (2H, m), 3.48-3.82 (2H, m).

Step 3

To a stirred solution of 1-t-butoxycarbonyl-4-(4-chlorophenyl)-4-hydroxyhomopiperidine (2.1 g) at RT in CH₂Cl₂ (48 mL) was added TFA (2.0 mL). The reaction was

stirred at RT for 2 hrs. Excess solvent and TFA was removed affording 2.0 g (92% yield) 1:1 mixture of 3-(4-chlorophenyl)-2,3-dehydrohomopiperidine and 3-(4-chlorophenyl)-3,4-dehydrohomopiperidine. ¹H NMR (MeOD,

CDCl₃, 2.01-2.11 (2H, m, 4), 2.60-2.71 (2H, m, 5), 2.81-2.92 (2H, m, 4), 2.83-3.05 (2H, m, 5), 3.66-3.92 (4H, m, 5), 6.16-6.21 (1H, t, 5). ¹H NMR (MeOD, isomer B) 3.44-3.56 (2H, m, 4), 3.88-3.97 (2H, m, 4), 6.01-6.12 (1H, t, 4), 7.32-7.44 (1H, t, 4).

Step 4

The compounds can be prepared by following the procedure for Example 44 but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3,4-dehydrohomopiperidine and 3-(4-chlorophenyl)-4-

dehydrohomopiperidine and 3-(4-chlorophenyl)-4,5-dehydrohomopiperidine.

Step 5

To a cold (0°C) stirred solution of 1-t-butoxycarbonyl-4-oxohomopiperidine (1.42 g, 6.07 mmol) in anhydrous THF (50

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Example 255

1-(4-Chlorophenyl)-4-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperazinone

5 The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)piperazinone.

H-NMR (CDCl_3) δ : 2.30-2.34(2H,m), 2,49-2.57(2H,m), 6.05(2H,t), 3.06(2H,s), 3.58(2H,t), 5,12(2H,brs), 6.05(2H,t), 6.57-6.69(3H,m), 7.35-7.71(5H,m), 7.72(1H,dd), 8.48(1H,dd).

MS m/z: 503(M+1)

Example 261

1'-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]spiro[5-chloro-1,3-benzodioxole-2,4'-piperidine]

15 The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-ylidene)propyl]homopiperazine with 1-(4-

chlorophenyl)-4-hydroxypiperidine with 1-(4-ylidene)propyl]homopiperazine.

20 The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with spiro[5-chloro-1,3-benzodioxole-2,4'-piperidine] (*Journal of Medicinal Chemistry*. 1995, 38, 2009-2017).

H-NMR (CDCl_3) δ : 1.89(2H,brs), 2.27-2.35(2H,m), 2.51-2.70(6H,m), 3.37-3.53(4H,m), 5.23(2H,brs), 5.98(1H,t), 6.48-6.74(6H,m), 7.05-7.26(2H,m), 7.52(1H,dd), 8.45(1H,dd).

25 **MS m/z:** 462(M+1)

Example 260

3-(4-Chlorophenyl)-8-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-8-azabicyclo[3.2.1]octan-3-ol

To a solution of the product of example 211 (330mg)

and in acetonitrile (1.2mL) was added iodomethane

The titled compound was prepared by following the procedure of example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol

$^1\text{H-NMR}$ (CDCl_3) δ : 3.1.65-2.10(4H,m), 2.1-2.7(8H,m), 3.32(2H,bs), 3.78(3H,s), 5.24(2H,bs), 6.10(1H,dd), 6.70-6.90(3H,m), 7.15-7.31(3H,m), 7.45(bd,2H), 7.64(dd,1H) 8.46(dd,1H)

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(0.07ml), and the reaction mixture was stirred at room temperature for 2 hours. The precipitation was filtered and washed with acetonitrile to give the titled compound

5 H-NMR (DMSO-d₆) δ: 1.39 (6H, s), 1.65-1.85 (2H, m),

¹H-NMR (DMSO-d₆) δ: 1.75-1.80(2H, m), 2.38-2.50(2H, m), 2.63-2.73(2H, m), 2.78(3H,d), 3.17-3.50(6H, m), 5.38(2H, brs), 6.36(1H, t), 6.87(1H, d), 7.41-7.50(4H, m), 7.55-7.99(4H, m), 8.48-8.50(1H, m), 8.61(1H, dd).

2.20-2.64 (4H,m), 3.09 (3H,s), 3.30-3.65 (6H,m), 5.20 (2H,m),
 5.61 (1H,s), 6.01 (1H,t), 6.75-6.92 (3H,m), 7.27 (1H,s),
 7.38-7.64 (6H,m), 7.83 (1H,dd), 8.56 (1H,dd)

4-(4-Chlorophenyl)-1-[3-(7-diethylaminocarbonylmethoxy-

5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine

¹hydrochloride with diethylamine.
H-NMR (CDCl₃) δ: 1.67-1.72 (2H,m), 1.99-2.10 (2H,m),
2.36-2.70 (9H,m), 2.89 (3H,d), 4.45 (2H,s), 5.28 (2H,brs),
6.08 (1H,t), 6.66 (1H,brs), 6.73-6.84 (3H,m),
7.25-7.45 (5H,m), 7.58 (1H,dd), 8.47 (1H,dd).
MS m/z: 534 [M+]
20

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7methy]amino]carboxyyl[1]benzoxepin-8[2,3- β]oxyridin-5-

25 ylidene)propyl)piperidin-4-ol

The title compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with methylamine.

Example 270
4-(4-Chlorophenyl)-1-[3-(7-diethylaminocarbonyl-5, 11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol
The titled compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with diethylamine.
MS m/z: 546(M+1)

Example 273
 4-(4-Chlorophenyl)-1-[3-({5,11-dihydro-7-
 (methoxycarbonyl)benzoxepino[2,3-b]pyridin-5-
 ylidene}propyl)piperidin-4-ol

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A mixture of the product of example 169 (15.0g), palladium(II) diacetate (170mg), 1,3-bis(diphenylphosphino)propane (310mg), and triethylamine (7.0ml) in methanol (100ml) and dimethylformamide (150ml) was purged with carbon monoxide for 5 minutes and stirred under a carbon monoxide balloon at 70°C for 8 hours. The reaction mixture was evaporated under reduced pressure. The residue was added water and extracted with ethyl acetate. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : methanol = 10:1) to give the titled compound (13.1g).

¹H-NMR (CDCl₃) δ: 1.45-1.80 (3H, m), 1.90-2.15 (2H, m),

2.28-2.48 (4H, m), 2.50-2.75 (4H, m), 3.89 (3H, s),

5.25-5.50 (2H, m), 6.20 (1H, dd), 6.85 (1H, d), 7.20-7.37 (3H, m), 7.42 (2H, d), 7.58 (1H, d), 7.80 (1H, dd), 8.01 (1H, dd), 8.52 (1H, dd)

MS m/z: 505 (M+1)

Example 275

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-propylamino)methyl [1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of example 314 (300mg)

and 1-propylamine (0.26ml) in tetrahydrofuran (6 ml) was added acetic acid (0.36ml), and the reaction mixture was

stirred at 60°C for 30 minutes. Then the reaction

mixture was added sodium triacetoxyborohydride (670mg) at 0°C, and stirred for 1.5 hours at room temperature. Sodium bicarbonate, water, and chloroform were added to the reaction mixture. The organic layer was extracted, and dried over potassium carbonate, and evaporated under reduced pressure. The residue was recrystallized with

25 ethyl acetate to give titled compound (130mg).

¹H-NMR (CDCl₃) δ: 0.92 (3H, t), 1.49-1.70 (6H, m), 1.98 (2H, m), 2.34-2.42 (4H, m), 2.51-2.70 (6H, m), 3.71 (2H, s), 5.32 (2H, brs), 6.12 (1H, t), 6.81 (1H, d), 7.11 (1H, dd), 7.25-7.45 (6H, m), 7.57 (1H, dd), 8.49 (1H, dd),

MS m/z: 518 (M+1)

and the filtrate was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform: methanol : 28% ammonia in water = 100 : 5 : 1) to give the titled compound (1.6g).

¹H-NMR (CDCl₃) δ: 1.55-1.71 (3H, m), 1.95-2.25 (2H, m), 2.34-2.70 (8H, m), 4.62 (2H, s), 5.20-5.45 (2H, brs), 6.13 (1H, t), 6.84 (1H, d), 7.16 (1H, dd), 7.23-7.43 (6H, m), 7.58 (1H, dd), 8.51 (1H, dd)

MS m/z: 477 (M+1)

Example 274

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-hydroxymethyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To an ice-cooled solution of the product of example

25 273 (2.0g) in tetrahydrofuran (100ml) was added lithium aluminum hydride (300mg), and the reaction mixture was

stirred at room temperature for 12 hours. After the reaction mixture was cooled to 0°C, water (0.3ml), 15% sodium hydroxide aqueous solution (0.3ml), and water (0.9ml) were added. The reaction mixture was filtered,

30 and the solvent was evaporated under reduced pressure.

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Example 276.

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-hydroxy-1-propylamino)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 275, but replacing 1-propylamine with 3-amino-1-propanol.

MS m/z: 534 (M+1)

Example 277

10 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-piperidino)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 275, but replacing 1-propylamine with 15 piperidine.

MS m/z: 544 (M+1)

Example 278

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-morpholinomethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 275, but replacing 1-propylamine with morpholine.

MS m/z: 546 (M+1)

Example 279

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-pyrrolidino)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 275, but replacing 1-propylamine with morpholine.

MS m/z: 546 (M+1)

Example 280

10 Example 280
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 273, but replacing the product of

¹example with the product of example 274.

¹H-NMR (CDCl₃) δ: 1.60-1.70 (4H, m), 2.01-2.12 (2H, m), 2.37-2.70 (8H, m), 2.81 (2H, t), 3.84 (2H, t), 5.31 (2H, brs), 6.09 (1H, t), 6.81 (1H, d), 7.03 (1H, dd), 7.15 (1H, d), 7.26-7.43 (5H, m), 7.57 (1H, dd), 8.49 (1H, dd).

MS m/z: 491 (M+1)

25 Example 279
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-pyrrolidino)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 272, but replacing dimethylamine hydrochloride with ammonium hydroxide.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H, m), 1.98-2.06 (2H, m),

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2.27-2.70(9H, m), 3.46(2H, s), 5.30(2H, brs), 5.74(1H, brs),
 6.04(1H, brs), 6.09(1H, t), 6.79(1H, d), 7.02(1H, dd),
 7.18-7.41(6H, m), 7.54(1H, dd), 8.43(1H, dd).
 MS m/z: 504(M+1)

5 Example 288

4-(4-Chlorophenyl)-1-[3-(7-(2-ethoxycarboxy)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 165, but replacing the product of example 164 with the product of example 310.

¹H-NMR (CDCl₃) δ: 1.23(3H, t), 1.63-1.71(3H, m), 1.98-2.10(2H, m), 2.35-2.71(10H, m), 2.89(2H, t), 4.13(2H, q), 5.31(2H, brs), 6.08(1H, t), 6.78(1H, d), 7.00(1H, dd), 7.12(1H, d), 7.26-7.44(5H, m), 7.57(1H, dd), 8.49(1H, dd). MS m/z: 548(M+1)

Example 289

4-(4-Chlorophenyl)-1-[3-(7-(1-(3-hydroxy)propyl)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 288.

¹H-NMR (DMSO-d₆) δ: 1.45-1.50(2H, m), 1.66-1.80(4H, m), 2.26-2.57(10H, m), 3.41(2H, q), 4.46(1H, t), 4.83(1H, s), 5.23(2H, brs), 6.14(1H, t), 6.71(1H, d), 7.01(1H, dd), 7.13(1H, d), 7.34-7.48(5H, m), 7.72(1H, dd), 8.49(1H, dd). MS m/z: 505(M+1)

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Example 290

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,3-dihydroxy)propyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of product of example 170 (6.9g) in tetrahydrofuran (70ml) and water (14ml) were added N-methylmorpholine oxide(1.7g) and osmium tetroxide at 0°C, and the mixture was stirred at room temperature for 3 hours. Ethyl acetate was added to the mixture, the aqueous layer was separated. Chloroform-isopropanol (4:1) was added to the aqueous layer, the organic layer was extracted, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure to give the titled compound (7.0g).

¹H-NMR (CDCl₃) δ: 1.65-1.73(2H, m), 1.95-2.10(2H, m), 2.30-2.75(13H, m), 3.45-3.50(1H, m), 3.60-3.65(1H, m), 3.83-3.90(1H, m), 5.28(2H, brs), 6.06(1H, t), 6.84(1H, d), 7.03(1H, dd), 7.15(1H, d), 7.26-7.43(5H, m), 7.57(1H, dd), 8.49(1H, dd). MS m/z: 521(M+1)

Example 291

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-phenyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 170, but replacing allyltributyltin with phenyltributyltin.

¹H-NMR (CDCl₃) δ: 1.84-1.92(2H, m), 2.85-3.40(10H, m), 5.33(2H, brs), 6.05(1H, t), 6.95(1H, d), 7.30-7.58(12H, m), 7.63-7.66(1H, m), 8.56-8.58(1H, m)

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MS m/z: 523 (M+1)

Example 292

4-(4-Chlorophenyl)-1-[3-(7-(2-furyl)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 170, but replacing allyltributyltin with ethyl (2-furyl)tributyltin.

¹H-NMR (CDCl₃) δ: 1.70-1.80 (3H, m), 1.97-2.16 (2H, m), 2.3-2.8 (8H, m), 5.36 (2H, m), 6.19 (1H, t), 6.45 (1H, dd), 6.55 (1H, d), 6.87 (1H, d), 7.20-7.50 (7H, m), 7.60-7.65 (2H, m), 8.52 (1H, dd)

MS m/z: 513 (M+1)

Example 293 - 4-(4-Chlorophenyl)-1-[3-(7-ethoxycarbonylamino-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

A mixture of product of example 118 (490mg) and diphenylphosphonic azide (0.28ml) was stirred at 110°C for 30 minutes. After the mixture was cooled, and triethylamine (0.14ml) and ethanol (5ml) were added, and the mixture was heated to reflux for 8 hours. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was washed with saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to give the titled compound (210mg).

1H-NMR (CDCl₃) δ: 1.31 (3H, t), 1.65-1.70 (2H, m),

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2.01-2.09 (2H, m), 2.36-2.70 (8H, m), 4.21 (2H, q), 5.30 (2H, brs), 6.13 (1H, t), 6.46 (1H, brs), 6.80 (1H, d), 7.02 (1H, dd), 7.28-7.50 (6H, m), 7.57 (1H, dd), 8.50 (1H, dd).

MS m/z: 534 (M+H)

Example 294

1-[Bis(ethoxycarbonylmethyl)methoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with diethyl bromomalonate.

¹H-NMR (CDCl₃) δ: 1.30 (3H, t), 1.66-1.71 (2H, m), 1.98-2.09 (2H, m), 2.35-2.69 (9H, m), 4.30 (2H, q), 5.14 (1H, s), 5.26 (2H, brs), 6.10 (1H, t), 6.78 (2H, d), 7.00 (1H, t), 7.26-7.45 (5H, m), 7.57 (1H, dd), 8.43 (1H, dd).

MS m/z: 621 (M+1)

Example 295

1-[1,1-Bis(ethoxycarbonylmethyl)ethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with diethyl 2-bromo-2-methylmalonate.

¹H-NMR (CDCl₃) δ: 1.27 (6H, t), 1.65-1.70 (5H, m), 1.99-2.08 (3H, m), 2.31-2.69 (8H, m), 4.28 (4H, q), 5.27 (2H, brs), 6.06 (1H, t), 6.72 (1H, d), 6.80 (1H, dd), 7.00 (1H, d), 7.27-7.45 (5H, m), 7.56 (1H, dd), 8.46 (1H, dd).

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4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxy-1-hydroxymethyl)ethoxy]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of example 294.

¹H-NMR (CDCl₃) δ: 1.70-1.75 (2H, m), 2.10-2.80 (11H, m), 3.90 (4H, d), 4.36 (1H, quint), 5.28 (2H, brs), 6.13 (1H, t), 6.71-6.87 (2H, m), 7.00 (1H, d), 7.29-7.45 (5H, m), 7.58 (1H, dd), 8.51 (1H, dd).

MS m/z: 537 (M+1)

Example 297

1-[1,1-Bis(hydroxymethyl)ethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)-piperidin-4-ol

The titled compound was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of example 295.

¹H-NMR (CDCl₃) δ: 1.09 (3H, s), 1.66-1.71 (2H, m), 1.90-2.10 (3H, m), 2.37-2.75 (8H, m), 3.72-3.82 (4H, m), 5.29 (2H, brs), 6.05 (1H, t), 6.77 (1H, d), 6.88 (1H, dd), 7.03 (1H, d), 7.26-7.43 (5H, m), 7.56 (1H, dd), 8.48 (1H, dd).

MS m/z: 551 (M+1)

Example 298

1-[3-(7-(3-Carboxy-1-propyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 299.

¹H-NMR (DMSO-d6) δ: 1.41-1.95 (2H, m), 1.41-1.95 (4H, m), 2.20-2.72 (10H, m), 3.95 (2H, t), 5.18 (2H, brs), 6.17 (1H, t), 6.72-6.84 (3H, m), 7.36-7.48 (5H, m), 7.77 (1H, dd), 8.50 (1H, dd).

MS m/z: 549 (M+1)

Example 300

1-[3-(7-(3-Carboxy-1-propyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 299.

¹H-NMR (DMSO-d6) δ: 1.41-1.95 (2H, m), 1.41-1.95 (4H, m), 2.20-2.72 (10H, m), 3.95 (2H, t), 5.18 (2H, brs), 6.17 (1H, t), 6.72-6.84 (3H, m), 7.36-7.48 (5H, m), 7.77 (1H, dd), 8.50 (1H, dd).

Example 301

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-methoxycarbonylphenyl)methoxy]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with methyl 4-bromomethylbenzoate.

¹H-NMR (CDCl₃) δ: 1.66-1.70 (2H, m), 1.93-2.09 (3H, m), 2.37-2.70 (8H, m), 3.91 (2H, s), 5.09 (2H, s), 5.27 (2H, brs), 6.06 (1H, t), 6.80-6.91 (3H, m), 7.24-7.60 (8H, m), 8.01-8.07 (2H, m), 8.47 (1H, dd).

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Example 302
 1-[3-(7-(4-Carboxyphenyl)methoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

5 The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of example 301.

¹H-NMR (DMSO-d₆) δ: 1.44-1.49 (2H, m), 1.67-1.87 (2H, m), 2.26-2.56 (8H, m), 4.85 (1H, brs), 5.15-5.25 (4H, m), 6.17 (1H, t), 6.72-6.95 (3H, m), 7.30-7.75 (8H, m), 7.92-7.99 (2H, m), 8.48 (1H, dd).
 MS m/z: 597 (M+1)

Example 303

15 hydroxymethyl)cyclopropyl)methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

1-[3-(7-(1-Benzoyloxymethyl)cyclopropyl)methoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol was prepared by following the procedure of example 46, but replacing ethyl iodide with (1-benzoyloxymethyl)cyclopropylmethyl methanesulfonate.

¹H-NMR (CDCl₃) δ: 0.70-0.81 (4H, m), 1.65-1.70 (3H, m), 1.98-2.07 (2H, m), 2.35-2.70 (8H, m), 3.91 (2H, s), 4.39 (2H, s), 5.25 (2H, brs), 6.06 (1H, t), 6.72-6.84 (3H, m), 7.23-7.59 (9H, m), 8.02-8.05 (2H, m), 8.48 (1H, dd).

Step 2
30 The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

¹H-NMR (CDCl₃) δ: 0.62 (4H, s), 1.67-1.72 (2H, m), 1.96-2.06 (2H, m), 2.34-2.69 (8H, m), 3.39 (1H, brs), 3.91 (2H, s), 3.91 (2H, s), 5.26 (2H, brs), 6.09 (1H, t), 6.72-6.86 (3H, m), 7.27-7.60 (6H, m), 8.48 (1H, dd).
 MS m/z: 547 (M+1)

Example 305

1-[3-(5,11-dihydro-7-(2-hydroxyethyl)amino carbonyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

10 The titled compound was prepared by following the procedure of example 198, but replacing dimethylamine hydrochloride with 2-hydroxyethylamine.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H, m), 2.03-2.06 (2H, m), 2.21 (1H, d), 2.32-2.68 (8H, m), 3.63 (2H, dt), 3.83 (2H, t), 5.37 (2H, brs), 6.18 (1H, t), 6.67 (1H, brs), 7.25-7.54 (7H, m), 7.86 (1H, dd), 8.50 (1H, dd).
 MS m/z: 534 (M+1)

Example 306

20 cyclohexyloxycarbonyloxy)ethyloxycarbonyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol dihydrochloride

To a solution of product of example 118 (1.1g) in dimethylformamide (15mL) were added sodium iodide (0.17g), 25 potassium carbonate (0.38 g) and cyclohexyl 1-chloroethyl carbonate (*J. Antibiotics*, 1987, 40, 81.) (0.57g) at room temperature. The mixture was stirred at 70°C for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with 30 saturated aqueous sodium chloride, and dried with

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magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate : methanol = 100 : 3). The obtained oil was dissolved with ethyl acetate, 5 and 4 N hydrochloric acid ethyl acetate solution (0.8ml) was added. The precipitation was filtered to give the titled compound (0.95g).

¹H-NMR (DMSO-d₆) δ: 1.22-1.47(6H,m), 1.58(3H,d),

1.63-1.81(6H,m), 2.38-3.30(10H,m), 4.07-4.59(1H,m),

5.80(2H,brs), 6.28(1H,t), 6.87(1H,q), 6.97(1H,d),

7.40-7.49(4H,m), 7.64(1H,dd), 7.79(1H,dd), 7.96(1H,d),

8.03(1H,dd), 8.65(1H,dd), 11.07(1H,brs).

MS m/z: 661[(M-2HCl)+]

Example 307

15 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7(1-ethoxycarbonyloxy)ethyloxycarbonyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 307, but replacing cyclohexyl 1-

20 chloroethyl carbonate with ethyl 1-chloroethyl carbonate. MS m/z: 667(M+1)

Example 308

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(5-hydroxifuran-2-yl)[1]benzoxepino[2,3-b]pyridin-5-

25 ylidene)propyl]piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(5-formylfuran-2-yl)[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidin-4-ol was prepared by following

the procedure of example 170, but replacing allyltributyltin with (5-formylfuran-2-yl)tributyltin.

¹H-NMR (CDCl₃) δ: 1.40-1.80(2H,m), 1.89-2.12(2H,m), 2.20-2.75(8H,m), 5.28(2H,brs), 6.16(1H,t), 6.69(1H,d), 6.84(1H,d), 7.22-7.55(8H,m), 7.76(1H,d), 8.42(1H,dd), 9.52(1H,s).

Step 2

The titled compound was prepared by following the procedure of example 199, but replacing the product of example 138 with the product of step 1.

MS m/z: 543(M+1)

Example 309

1-[3-(7-(5-Carboxyfuran-2-yl)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

20 ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 382, step 2, but replacing the product of Example 382, step 1 with the product of example 307, step 1.

MS m/z: 557(M+1)

Example 310

4-(4-Chlorophenyl)-1-[3-(7-(2-ethoxycarbony)ethenyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

25 ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 171, but replacing t-butyl acrylate with ethyl acrylate.

¹H-NMR (CDCl₃) δ: 1.33(3H,t), 1.63-1.71(3H,m), 1.98-2.10(2H,m), 2.35-2.72(8H,m), 4.25(2H,q),

30 5.36(2H,brs), 6.10(1H,t), 6.33(1H,d), 6.85(1H,d),

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7.22-7.44 (7H, m), 7.58-7.65 (2H, m), 8.53 (1H, dd).

Example 311

4-(4-Chlorophenyl)-1-[3-(7-(1-(2-ethyl-2-hydroxy)butyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 200, but replacing ethylmagnesium bromide with methylmagnesium bromide.

¹H-NMR (CDCl_3) δ : 0.93 (6H, t), 1.60-1.70 (6H, m), 1.95-2.10 (3H, m), 2.36-2.70 (8H, m), 3.79 (2H, s), 5.28 (2H, brs), 7.24-7.43 (5H, m), 7.57 (1H, dd), 8.47 (1H, dd).
MS m/z: 563 (M+1)

Example 312

4-(4-Chlorophenyl)-1-[3-(7-(2,3-dimethyl-3-hydroxybutyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 200, but replacing the product of example 48 with the product of example 138.

¹H-NMR (CDCl_3) δ : 1.22 (6H, s), 1.32 (6H, s), 1.66-1.71 (2H, m), 1.99-2.10 (2H, m), 2.35-2.85 (9H, m), 3.77 (2H, s), 5.28 (2H, brs), 6.04 (1H, t), 6.74-6.89 (3H, m), 7.26-7.43 (5H, m), 7.57 (1H, dd), 8.44 (1H, dd).
MS m/z: 563 (M+1)

Example 313

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-oxopropyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

⁵ The titled compound was prepared by following the procedure of example 146, but replacing ethyl iodide with chloroacetone.

¹H-NMR (CDCl_3) δ : 1.62-1.71 (3H, m), 1.99-2.10 (2H, m), 2.27 (3H, s), 2.35-2.70 (8H, m), 4.51 (2H, s), 5.28 (2H, brs), 6.08 (1H, t), 6.70-6.84 (3H, m), 7.25-7.32 (3H, m), 7.44 (2H, m), 7.58 (1H, dd), 8.50 (1H, dd).
MS m/z: 519 (M+1)

Example 314

4-(4-Chlorophenyl)-1-[3-(7-formyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of example 274 (1.0g) in methylene chloride (200ml) was added manganese(IV) oxide (3.0g), and the suspension was stirred at ambient temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The solvent was evaporated under reduced pressure to give the titled compound (930mg).

¹H-NMR (CDCl_3) δ : 1.71-1.80 (3H, m), 1.98-2.09 (2H, m), 2.35-2.43 (4H, m), 2.53-2.69 (4H, m), 5.30 (2H, brs), 6.24 (1H, t), 6.95 (1H, d), 7.27-7.44 (5H, m), 7.61 (1H, dd), 7.67 (1H, dd), 7.85 (1H, d), 8.54 (1H, dd), 9.88 (1H, s).

Example 315

1-[3-(7-Acetyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

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Step 1

To a solution of example 53, step 1 (7.2g) in dichloromethane (70 mL) was added aluminum chloride (9.1 g) and acetyl chloride (3.2 mL), and the mixture stirred at 0°C for 10 minutes. The reaction mixture was poured into ice. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography, eluting with ethyl acetate-hexane (1:2) to give 7-acetyl-1,5-(3-bromopropylidene)-5,11-dihydro[1]benzoxepino[2,3-b]pyridine (7.9 g).

¹H-NMR (CDCl₃) δ: 2.57(3H, s), 2.77(2H, m), 3.49(2H, t), 5.40(2H, brs), 6.16(1H, t), 6.88(1H, d), 8.33(1H, dd), 7.58(1H, dd), 7.77(1H, dd), 7.96(1H, d), 8.56(1H, dd).

Step 2

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.52-1.79(2H, m), 1.93-2.11(2H, m), 2.27-2.49(4H, m), 2.49-2.60(5H, m), 2.60-2.73(2H, m), 5.40(2H, brs), 6.22(1H, t), 6.87(1H, d), 7.29-7.34(3H, m), 7.42(2H, d), 7.59(1H, dd), 7.75(1H, dd), 7.96(1H, d), 8.53(1H, d).

MS m/z: 489(M+1)

Example 316

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K₂CO₃ (1.5 mmol) in THF (10 mL) at RT was added N-methyl-N-phenylcarbamoylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH₂Cl₂.

The reaction was stirred at reflux for 24 hrs. Excess

solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH₂Cl₂. MS m/z: (M⁺ 535)

Step 3

Example 317

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K₂CO₃ (1.5 mmol) in THF (10 mL) at RT was added morpholinocarbamoylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH₂Cl₂. MS m/z: (M⁺ 577)

Example 318

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) in DMF at RT was added NaH (1.5 mmol) followed by the addition of N-isopropylisocyanate (1.5 mmol). The reaction was heated to 60°C for 6 hrs. The reaction was quenched with 1.5 equivalents of H₂O and excess DMF was removed under reduced pressure. Residue was charged on a silica gel column and eluted off with 5% MeOH/CH₂Cl₂. MS m/z: (M+548)

Example 319

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K₂CO₃ (1.5 mmol) in THF (10 mL) at RT was added N-methyl-N-phenylcarbamoylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH₂Cl₂. MS m/z: (M⁺ 597)

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Example 320

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) in DMF at RT was added NaH (1.5 mmol) followed by the addition of *N*-phenylisocyanate (1.5 mmol). The reaction was heated to 60°C for 6 hrs. The reaction was quenched with 1.5 equivalents of H₂O and excess DMF was removed under reduced pressure. Residue was charged on a silica gel column and eluted off with 5% MeOH/CH₂Cl₂. MS m/z: (M⁺ 583)

Example 321

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) in DMF at RT was added NaH (1.5 mmol) followed by the addition of *N*-(3-pyridyl)isocyanate (1.5 mmol). The reaction was heated to 60°C for 6 hrs. The reaction was quenched with 1.5 equivalents of H₂O and excess DMF was removed under reduced pressure. Residue was charged on a silica gel column and eluted off with 5% MeOH/CH₂Cl₂. MS m/z: (M⁺ 584)

Example 322

To a stirred solution of phenol containing the product of Example 44 (1.0 mmol) and K₂CO₃ (1.5 mmol) in THF (10 mL) at RT was added pyrrolidinyloxycarbonylchloride (1.2 mmol). The reaction was stirred at reflux for 24 hrs. Excess solvent was removed and pure compound was isolated via silica gel chromatography eluting with 5% MeOH/CH₂Cl₂.

MS m/z: (M⁺ 560)

Example 323

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-cyanopiperidine. MS m/z: (M⁺ 486).

Example 324

To a cold (0°C) stirred solution of Example 323 (0.50 g, 0.104 mmol) in anhydrous THF (5 mL) was added lithium aluminum hydride (8 mg, 0.21 mmol). The reaction was stirred at RT for 2 hrs. The reaction was then quenched by the careful addition of H₂O (0.21 mL), 15% aqueous KOH (0.21 mL), then H₂O (0.21 mL). The organic layer was separated and dried over Na₂SO₄. The compound was purified via silica gel flash chromatography eluting with 10% methanol/methylene chloride. MS m/z: (M⁺ 490).

Example 325

The compound can be obtained by the reduction of the azido functionality of Example 187 with a reducing agent, such as triphenyl phosphine, lithium aluminum hydride, sodium borohydride, in a solvent such as tetrahydrofuran or diethyl ether in reaction temperature ranges from 0°C to reflux with a reaction time between 5 minutes and 72 hours.

Example 326

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-methylpiperidine provide in Example 329, steps 1-3. MS m/z: (M⁺ 475)

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Example 328

Step 1

N-benzyl-4-(4-chlorophenyl)-4-hydroxypiperidine: Fig. 8a
 To a stirred solution of commercially available 4-(4-chlorophenyl)-4-hydroxypiperidine (10 g, 47 mmol., 1) in anhydrous DMF (10 mL) was added benzyl bromide (5.6 mL, 47 mmol.) and K_2CO_3 (7.4 g, 94 mmol.) and stirred at RT overnight. Excess solvent was removed under reduced pressure, brought up into CH_2Cl_2 (100 mL) washed with H_2O (2 X 50 mL). Organic layer separated, dried over Na_2SO_4 and charged on a silica gel flash column. Eluting off with 2% MeOH/ CH_2Cl_2 , 10 g 2 (80% yield) was obtained as a viscous liquid. MS m/z: (M^+ 303)

Step 2

N-benzyl-4-(4-chlorophenyl)-4-fluoropiperidine: Fig. 8a
 To a cold (-78°C) solution of 2 (10 g, 33 mmol) in CH_2Cl_2 (20 mL) was slowly added DAST (diethylaminosulfur trifluoride, 5.3 mL, 39.8 mmol) under an inert atmosphere. The reaction was stirred at -78°C for an additional 45 min. The reaction was quenched at -78°C by the slow addition of enough saturated aqueous sodium bicarbonate solution to afford a pH >8. This reaction resulted a quantitative conversion of the starting material to a 1:1 mixture of fluoropiperidine 3 and 4-(4-

chlorophenyl)tetrahydropyridine 4. The mixture of 3 and 4 (3.5 g, mixture, ~35% yield) was purified via silica gel flash chromatography, eluting with 2% MeOH/ CH_2Cl_2 . This mixture proved to be inseparable by silica gel flash chromatography. In order to separate out the desired product, the mixture of 3 and 4 were subjected to osmium tetroxide oxidation.

To a stirred solution of the mixture of 3 and 4 (1.8 g) in acetone/ H_2O (5:1, 10 mL) was added a catalytic amount of OSO_4 in isopropanol (2.5 mol %, 1 mL) and N-methylmorpholine-N-oxide (0.69 g, 6.56 mmol). The reaction was stirred at RT overnight. The reaction was then evaporated to dryness, brought up into CH_2Cl_2 and washed with $NaHSO_3$. This reaction resulted in the dihydroxylation of the undesired 4 to 5 and the clean separation of the desired fluoropiperidine 3 (1.0 g, 55% yield) from the byproduct by silica gel flash chromatography eluting with 2% MeOH/ CH_2Cl_2 . MS m/z: (M^+306)

Step 3

4-(4-chlorophenyl)-4-fluoropiperidine: Fig. 8a

To a cold (0°C) solution of 3 (1.07 g, 3.5 mmol) in 1,2-dichloroethane was added 1,1-chloroethylchloroformate (0.45 mL, 4.2 mmol). The reaction was then heated to reflux for 2 hrs. Excess solvent was removed and the residue was brought up into 5 mL methanol. The mixture was refluxed for 2 hrs and excess methanol was removed under reduced pressure. Precipitation of the hydrochloride salt of 6 by the addition of CH_2Cl_2 /hexane (1:1) followed by filtration resulted in the quantitative isolation of the desired crystalline product 6 (80%, 0.70 g). MS m/z: (M^+215)

Step 4

The compound was prepared by following the procedure for example 44, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-fluoropiperidine. MS m/z: (M^+ 466).

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Example 329

Step 1

N-benzyl-4-methylpiperidine: Fig. 8c

To a cold (-78°C) stirred solution of 1.4 M methylolithium 5 in THF (39 mL, 54 mmol) under an inert atmosphere was added *N*-benzyl-4-oxopiperidine (1, 5.1 g, 27 mmol). The reaction was stirred at -78°C for 2 hrs. The reaction was quenched by the slow addition of saturated aqueous NH₄Cl, the organic layer was separated and dried over Na₂SO₄.

Pure methylpiperidine (2) was isolated via silica gel flash chromatography eluting with 5% MeOH/CH₂Cl₂. MS m/z: (M+206)

Step 2

N-benzyl-4-(4-chlorophenyl)-4-methylpiperidine: Fig. 8c

To a flask containing chlorobenzene (10 mL, excess) and methylpiperidine (0.42 g, 2.06 mmol, 2) was added aluminum trichloride (1.65 mL, 12.4 mmol). The reaction was heated to reflux for 24 hrs. Excess chlorobenzene was removed under reduced pressure and pure 3 was obtained via silica gel flash chromatography eluting with EtOAc/hexane. MS m/z: (M+ 300)

Step 3

4-(4-chlorophenyl)-4-methylpiperidine: Fig. 8c

To a cold (0°C) solution of *N*-benzyl-4-(4-chlorophenyl)-4-methylpiperidine (3) (0.41 g, 1.4 mmol) in CH₂Cl₂ was 1.1 equivalent of 1-chloroethylchloroformate. The reaction was then heated to reflux for 2 hrs. Excess solvent was removed and the residue was brought up into methanol. The mixture was refluxed for 2 hrs and excess methanol was removed under reduced pressure. Precipitation of the hydrochloride salt 4 by the addition of CH₂Cl₂ followed by

filtration resulted in the quantitative isolation of the desired crystalline product 4 (100%, 0.34 g). MS m/z: (M+ 210)

Step 4

The compound was prepared by following the procedure for example 44, step 2, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-methylpiperidine. MS m/z: (M+ 461)

Example 330

10 The compound was prepared by following the procedure for example 199, but replacing the resultant compound of example 44 with the resultant compound of Example 329. MS m/z: (M+ 533)

Example 331

15 Step 1
A mixture of epichlorohydrin (5.92 g, 64 mmol) and benzhydrylamine (11.7 g, 64 mmol) in MeOH (120 mL) was stirred under the protection of argon at room temperature for 48 hours. The mixture was then stirred at 50°C for 72 hours. The reaction mixture was then stirred at room temperature for 72 hours. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and H₂O. The aqueous layer was extracted with EtOAc (200 mL x 3), dried over MgSO₄ and concentrated in vacuo.

25 Chromatographic purification on silica gel (CH₂Cl₂/MeOH = 95/5) provided 10.0 g (65%) of 1-benzhydryl-3-hydroxyazetidine. m/z 240 (m+1)

Step 2

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A mixture 1-benzhydryl-3-hydroxyazetidine (2.6 g, 11 mmol) and palladium hydroxide on active carbon (0.26 g, w/w 20%) in EtOH (40 mL) was shaken in hydrogenation Parr under 60 psi for 24 hours. The reaction mixture was filtered through celite and concentrated under vacuum.

Concentration in vacuo provided 0.75 (95%) 3-hydroxyazetidine. ^1H NMR (250 MHz, CD₃OD) 3.81-3.92 (2H, m), 4.14-4.25 (2H, m), 4.61-4.69 (1H, m).

Step 3

The compound 1-[3-(5,11-dihydro-7-

(methoxy[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]azetidin-3-ol was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-hydroxyazetidine.

Step 4

To a mixture of morpholine N-oxide (0.028 g, 0.244 mmol),

crushed molecular sieves (0.066 g) and Pr_nN⁺RO₄ (0.01 g, 0.024 mmol) in CH₂Cl₂, was added the 1-[3-(5,11-dihydro-7-

(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-ol (0.055 g, 0.16 mmol) under the protection of argon. The mixture was stirring over night at room temperature. The reaction mixture was filtered off through celite and concentrated under vacuum. Chromatographic purification on silica gel (CH₂Cl₂/MeOH = 95/5 to 9/1) provided 0.033 g 1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-one (60%) of the desired product. m/z 337 (m+1)

Example 332

Step 1

tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate: Fig. 10b

tert-Butyl N-(2-aminoethyl) carbamate (1, 0.50 g, 3.12 mmol) was added to the mixture of 4-chlorobenzoic acid chloride (0.547 g, 3.12 mmol) and Et₃N (1.74 mL, 12.5 mmol) in CH₂Cl₂ (20 mL) under the protection of argon. Stirring at room temperature for 2 hours. The reaction mixture was diluted with H₂O (25 mL), extracted with CH₂Cl₂ (50 mL x 2), dried over MgSO₄ and concentrated in vacuo. Chromatographic purification on silica gel (CH₂Cl₂/MeOH = 95/5) to provide 0.86 g (2, 93%) of the desired product tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate.

MS m/z: (M+ 299).
Step 2

Step 5

To a solution of 1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidin-3-one (0.06 g, 0.18 mmol) in THF (8 mL) was added dropwise a solution of 4-chlorophenyl magnesium bromide in diethyl ether (1.0 M, 0.27 mL) under the protection of argon at 0°C. The reaction was stirred at room temperature for 1.5 hours and quenched by the addition of saturated aqueous NH₄OH (4 mL). The aqueous layer was extracted with EtOAc (10 mL x 2), dried over MgSO₄ and concentrated in vacuo. Chromatographic purification on silica gel (CH₂Cl₂/MeOH = 95/5) provided 0.048 g 3-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]azetidine (51%) m/z 449 (m+1)

Step 2

Step 3

Step 4

tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate (51%) m/z 449 (m+1)

Step 5

Step 6

Step 7

tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate: Fig. 10c

tert-Butyl N-(2-aminoethyl) carbamate (1, 0.50 g, 3.12 mmol) was added to the mixture of 4-chlorobenzoic acid chloride (0.547 g, 3.12 mmol) and Et₃N (1.74 mL, 12.5 mmol) in CH₂Cl₂ (20 mL) under the protection of argon. Stirring at room temperature for 2 hours. The reaction mixture was diluted with H₂O (25 mL), extracted with CH₂Cl₂ (50 mL x 2), dried over MgSO₄ and concentrated in vacuo. Chromatographic purification on silica gel (CH₂Cl₂/MeOH = 95/5) to provide 0.86 g (2, 93%) of the desired product tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate.

MS m/z: (M+ 299).
Step 2

Step 5

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1-(4-chlorobenzoyl)-1,2-ethylenediamine: Fig. 10b
 Trifluoroacetic acid (7.5 mL) was added to the solution of
 tert-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl)carbamate
 (2, 0.86 g, 2.89 mmol) in CH₂Cl₂ (35 mL) at 0°C. Stirring
 at room temperature for 30 minutes. Concentration in
 vacuo provided 0.88 g (95%) of the desired product 1-(4-
 chlorobenzoyl)-1,2-ethylenediamine (3). MS m/z: (M+ 199).

Step 3

The compound was prepared by following the procedure for
 example 45, step 3, but replacing 4-(4-chlorophenyl)-4-
 hydroxypiperidine with 1-(4-chlorobenzoyl)-1,3-
 propylenediamine. MS m/z: (M+ 465).

Example 333**Step 1****2-(4-Chlorophenyl)-1-bromoethylene:** Fig. 9c

To a solution of AlCl₃ (1.96 g, 14.7 mmol) in anhydrous
 CH₂Cl₂ (50 mL), Borane-tert-butyl amine complex (2.57 g,
 29.6 mmol) was added at 0°C under argon protection, stirred
 for 10 minutes and clear solution was formed. 4-
 Chlorophenacyl bromide (1, 1.11 g, 4.91 mmol) in CH₂Cl₂ (5
 mL) was added to the resulted mixture at 0°C. The reaction
 was stirred for 1.5 hours and then quenched by the
 addition of 0.1 N HCl (25 mL). The mixture was extracted
 with EtOAc (80 mL x 3), dried over MgSO₄ and concentrated
 in vacuo. Chromatographic purification on silica gel
 (Hexane/EtOAc = 9:1) provided 0.85 g (84%) of 2-(4-
 chlorophenyl)-1-bromoethylene (2). MS m/z: (M+ 219).

Step 2**2-(4-chlorophenyl)-1-(N-methyl)ethylamine:** Fig. 9c

A mixture of 2-(4-chlorophenyl)-1-bromoethylene (2, 1.02
 g, 4.62 mmol), EtOH (3 mL) and H₂NMe in H₂O (6 mL, 40% w/w)
 was heated at 135 0°C over night. The mixture was cooled
 down to room temperature. The mixture was extracted with
 Et₂O (5mL x 2), dried over MgSO₄ and concentrated in vacuo.
 Chromatographic purification on silica gel
 (CH₂Cl₂/MeOH/NH₄OH = 9/1/0.1) provided 0.61 g 2-(4-
 chlorophenyl)-1-(N-methyl)ethylamine (3, 79%). MS m/z: (M+
 170).

10 Step 3

The compound was prepared by following the procedure for
 example 45, step 3, but replacing 4-(4-chlorophenyl)-4-
 hydroxypiperidine with 2-(4-chlorophenyl)-1-(N-
 methyl)ethylamine. MS m/z: (M+ 451).

Example 334**Step 1****3-(4-chlorophenyl)-1-N-methylaminopropane:** Fig. 9e

A mixture of 3-(4-chlorophenyl)-1-bromopropane (1, 0.70 g,
 3.73 mmol), EtOH (3 mL) and H₂NMe in H₂O (6 mL, 40% w/w)
 was heated at 135 0°C overnight. The mixture was then
 cooled down to room temperature. The mixture was
 extracted with Et₂O (5 mL x 2), dried over MgSO₄ and
 concentrated in vacuo. Chromatographic purification on
 silica gel (CH₂Cl₂/MeOH/NH₄OH = 9/1/0.1) provided 0.5 g
 (76%) of 3-(4-chlorophenyl)-1-N-methylaminopropane (2). MS
 m/z: (M+ 189).

Step 2

The compound was prepared by following the procedure for
 example 45, step 3, but replacing 4-(4-chlorophenyl)-4-

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hydroxypiperidine with 3-(4-chlorophenyl)-1-N-methylaminopropane. MS m/z: (M+ 450).

Example 335

Step 1

5 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane: Fig. 9d To 3,4'-Dichloropropylphenone (0.52 g, 2.53 mmol) in anhydrous MeOH (10 mL) at 0°C under the protection of argon, NaBH₄ (0.23 g, 3.03 mmol) was added to the solution by several portions. The reaction was stirred under the

same condition for 15 minutes. The mixture was warmed up to room temperature, stirred an additional 30 minutes, then concentration in vacuo. The residue was partitioned

between EtOAc and H₂O. The aqueous layer was re-extracted with EtOAc (30 mL x 2), dried over MgSO₄ and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 10/1) provided 1.0 g (85%) of 3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-bromopropane (2). MS m/z: (M+ 219).

Step 2

5 3-(4-chlorophenyl)-3-hydroxy-1-3-methyl-1-N-methylaminopropane: Fig. 10a A mixture of 3,3,3-(4-Chlorophenyl)-hydroxymethyl-1-bromopropane (2, 1.04 g, 4.74 mmol), EtOH (5 mL) and H₂NMe in H₂O (10 mL, 40% w/w) was heated at 135 0°C for 3 hours. The mixture was cooled down to room temperature. The mixture was extracted with Et₂O (5mL x 2), dried over MgSO₄, and concentrated in vacuo. Chromatographic purification on silica gel (CH₂Cl₂/MeOH/NH₂OH = 9/1/0.1) provided 1.01 g 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane. MS m/z: (M+ 205).

Step 2

The compound was prepared by following the procedure for

example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane. MS m/z: (M+ 481).

Step 3

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-hydroxy-1-3-methyl-1-N-methylaminopropane. MS m/z: (M+ 214).

Example 336

Step 1

25 3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-chloropropane:

Fig. 10a

To 3,4'-Dichloropropylphenone (1, 1.10 g, 5.40 mmol) in anhydrous THF at 0°C under the protection of argon, was

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added MemgBr (2.50 mL, 7.35 mmol) dropwise at 0°C. The reaction was stirred at room temperature for an additional hour. The reaction was quenched by adding saturated aqueous NH₄Cl. The reaction was then extracted with Et₂O (60 mL x 2), dried over MgSO₄ and concentrated in vacuo.

Chromatographic purification on silica gel (Hexane/EtOAc = 10/1) provided 1.0 g (85%) of 3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-bromopropane (2). MS m/z: (M+ 219).

Step 2

10 3-(4-chlorophenyl)-3-hydroxy-1-3-methyl-1-N-methylaminopropane: Fig. 10a

A mixture of 3,3,3-(4-Chlorophenyl)-hydroxymethyl-1-bromopropane (2, 1.04 g, 4.74 mmol), EtOH (5 mL) and H₂NMe in H₂O (10 mL, 40% w/w) was heated at 135 0°C for 3 hours. The mixture was cooled down to room temperature. The mixture was extracted with Et₂O (5mL x 2), dried over MgSO₄, and concentrated in vacuo. Chromatographic purification on silica gel (CH₂Cl₂/MeOH/NH₂OH = 9/1/0.1) provided 1.01 g 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane. MS m/z: (M+ 205).

Step 3

The compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-hydroxy-1-3-methyl-1-N-methylaminopropane. MS m/z: (M+ 480).

Example 345

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 1-azaxanthone, gives the desired compound.

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Example 346
Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 1-4-azifluorene, gives the desired compound.

5 Example 347

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 7-amino-1-azaxanthone, gives the desired compound.

Example 348

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 4,5-diazafluorene, gives the desired compound.

Example 349

Using the procedure of Example 45, but replacing 5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridin-5-one with 1-aza-7-nitroxanthone, gives the desired compound.

Example 350 -

3-(4-chlorophenyl)-1-[3-(5,11-dihydro-7-(methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]pyrrolidine

Step 1

A mixture of 1-benzyl-3-pyrrolidinone (10.0 g, 57 mmol), di-tert-butyl dicarbonate (13.7 g, 63 mmol) and palladium on active carbon (2.5 g, w/w 20%) in MeOH was shaken in a

Parr hydrogenation vessel (50 psi H₂) for 48 hours. The reaction mixture was filtered through celite and concentrated in vacuo. Chromatographic purification on

silica gel (Hexane/EtOAc = 1/1) provided 6.21 g 1-t-butoxycarbonyl-3-pyrrolidinone (59%). ¹H NMR (250 MHz, CDCl₃) 1.46 (9H, s), 2.57 (2H, t, J = 7.8 Hz), 3.71-3.75 (4H, m)

Step 2

To a stirred solution of 1-t-butoxycarbonyl-3-pyrrolidinone (0.57 g, 3.23 mmol) in THF (10 mL) was added 4-chlorophenyl magnesium bromide (1.0 M, 5.2 mL) under the protection of argon at 0°C. The reaction was stirred at

room temperature for 1 hour then quenched by the addition of saturated aqueous NH₄OH (8 mL). The aqueous layer was extracted with EtOAc (50 mL x 2), dried over MgSO₄, and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 3/1) provided 0.57 g 1-t-butoxycarbonyl-3-(4-chlorophenyl)-3-hydroxypyrrolidine (60%). m/z 298 (m+1)

Step 3

To a stirred solution of 1-t-butoxycarbonyl-3-(4-chlorophenyl)-3-hydroxypyrrolidine (0.335 g, 1.28 mmol) in

CH₂Cl₂ (8 mL) was added trifluoroacetic acid (2 mL) at 0°C slowly. The reaction was stirred at room temperature for 30 minutes and concentrated in vacuo. This provided 0.355 g 3-(4-chlorophenyl)-3-hydroxypyrrolidine (100%) the desired product. m/z 198 (m+1)

Step 4

The titled compound was prepared by following the procedure for example 44 but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 3-(4-chlorophenyl)-3-hydroxypyrrolidine. m/z 432 (m+1).

30 Example 351

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Step 1**4-(4-chlorophenyl)-4-pyridine: Fig 10d**

To a solution of 4-bromopyridine (1, 1.94 g, mmol), 4-chlorophenylboronic acid (2, 1.56 g, mmol) and K_2CO_3 (2.76 g, 2.0 equiv) in ethanol/toluene (5mL/100mL) was added Pd(PPh_3)₄. The reaction was refluxed for 1 hr, cooled back down to RT and quenched with H_2O (15 mL). The reaction mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4 . Pure 4-(4-chlorophenyl)-4-pyridine 2 (1.3g, 68% yield) was isolated after silica gel flash column purification eluting with 50% EtOAc/hexane. MS m/z: (M+191).

Step 2

The titled compound was prepared by following the procedure for example 45, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-pyridine. MS m/z: (M+456).

Example 352

The compound was prepared by following the procedure for example 44, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-pyridine. MS m/z: (M+442).

Example 352

The compound was prepared by following the procedure for example 44, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-chlorophenyl)-4-pyridine. MS m/z: (M+442).

Step 2
The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

1H-NMR ($CDCl_3$) δ : 1.36(3H, t), 1.65-2.07(4H, m), 2.32-2.63(8H, m), 4.34(2H, q), 5.33(2H, brs), 6.07(1H, t), 6.88-7.10(5H, m), 7.27-7.51(5H, m), 7.58(1H, dd), 7.97-8.00(2H, m), 8.49(1H, dd).

Example 353

5-(2-(N-(4-Chlorophenyl)-4-hydroxycyclohexyl)-N-methyl)ethylidene)-5,11-dihydro-7-methoxy[1]benzoxepino[2,3-b]pyridine

The compound was prepared by the procedure of Example 57, step 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-N-methyl-(4-chlorophenyl)-4-

hydroxycyclohexylamn. The starting material can be prepared according to methods disclosed in Journal of Medicinal Chemistry, Vol. 15, No. 12, pp.1239-1243 (1972).

Example 354
5-[3-(7-(4-Carboxyphenoxy)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-ethoxycarbonylphenoxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 2
The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with ethyl 4-fluorobenzoate

1H-NMR ($CDCl_3$) δ : 1.36(3H, t), 1.65-2.07(4H, m), 2.32-2.63(8H, m), 4.34(2H, q), 5.33(2H, brs), 6.07(1H, t), 6.88-7.10(5H, m), 7.27-7.51(5H, m), 7.58(1H, dd), 7.97-8.00(2H, m), 8.49(1H, dd).

Step 2
The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

1H-NMR ($CDMSO-d_6$) δ : 1.44-1.49(2H, m), 1.67-1.87(2H, m), 2.26-2.56(8H, m), 4.85(1H, brs), 5.29(2H, brs), 6.17(1H, t), 6.88-7.09(5H, m), 7.33-7.48(5H, m), 7.75(1H, dd), 7.89-7.93(2H, m), 8.52(1H, dd).
MS m/z: 582 (M)

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Example 355

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyimino)propyl)oxy][1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

To a solution of the product of example 313 (300mg) in ethanol (3,ml) was added hydroxylammonium chloride (80mg) at room temperature, and the mixture was stirred for 1 hour. The precipitation was filtered and washed with ethanol to give the titled compound (300mg).

¹H-NMR (DMSO-d₆) δ: 1.75-1.80 (2H,m), 2.23-2.42 (2H,m), 2.53 (3H,s) 3.16-3.48 (8H,m), 4.54 (2H,s), 5.19 (2H,brs), 5.57 (1H,s), 6.14 (1H,t), 6.76-6.98 (3H,m), 7.41-7.48 (5H,m), 7.79 (1H,dd), 8.53 (1H,dd), 10.93 (1H,s).
MS m/z: 515 (M+1)

Example 356

1-[3-(7-(2-Carboxy-2-methyl-1-propyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

20 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-ethoxycarbonyl-2-methylpropyl)oxy)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 354, but replacing the product of example 313 with the product of example 315.

¹H-NMR (DMSO-d₆) δ: 1.39-1.54 (2H,m), 1.64-1.86 (2H,m), 2.13 (3H,s), 2.19-2.36 (4H,m), 2.35-2.52 (4H,m), 4.83 (1H,s), 5.28 (2H,brs), 6.20 (1H,t), 6.80 (1H,d), 7.35 (2H,d), 7.43-7.49 (4H,m), 7.58 (1H,d), 7.76 (1H,d), 8.51 (1H,dd), 11.04 (1H,s).
MS m/z: 504 (M+1)

Example 358

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-propionyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

Step 2

¹H-NMR (CDCl₃) δ: 1.31 (6H,s), 1.67-1.72 (2H,m), 1.96-2.15 (2H,m), 2.39-2.78 (8H,m), 3.69 (3H,s), 3.93 (2H,s), 5.27 (2H,brs), 6.09 (1H,t), 6.70-6.83 (3H,m), 7.23-7.59 (6H,m), 8.46 (1H,dd).

Step 2

¹H-NMR (CDCl₃) δ: 1.22 (3H,t), 1.63-1.77 (2H,m), 1.97-2.13 (2H,m), 2.25-2.48 (4H,m), 2.48-2.60 (2H,m), 2.60-2.73 (2H,m), 2.96 (2H,q), 5.41 (2H,brs), 6.21

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of step 1.

¹H-NMR (DMSO-d₆) δ: 1.46-1.50 (2H,m), 1.74-1.85 (2H,m), 2.22-5.2.38 (8H,m), 3.92 (2H,s), 4.58 (1H,brs), 5.19 (2H,brs), 6.18 (1H,t), 6.71-6.83 (3H,m), 7.33-7.48 (5H,m), 7.72 (1H,dd), 8.49 (1H,dd).

MS m/z: 514 (M+1)

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5 (1H, t), 6.86 (1H, d), 7.30-7.34 (3H, m), 7.43 (2H, d),
 7.59 (1H, d), 7.75 (1H, dd), 7.97 (1H, d), 8.53 (1H, d).
 MS m/z: 503 (M+1)

Example 359

5 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-isobutyryl)benzoxepino[2,3-b]pyridin-5-ylidene]propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 315, but replacing acetyl chloride

10 with isobutyryl chloride.

¹H-NMR (CDCl₃) δ: 1.21-1.33 (2H, m), 1.76-2.00 (2H, m), 2.46-3.47 (BH, m), 3.53 (1H, m), 5.47 (2H, brs), 6.09 (1H, t), 6.89 (1H, d), 7.32-7.45 (6H, m), 7.64 (1H, d), 7.79 (1H, dd), 7.94 (1H, d), 8.57 (1H, d).

MS m/z: 517 (M+1)

Example 360

4-(4-Chlorophenyl)-1-[3-(7-cyclopropylacetyl)-5,11-dihydro-11benzoxepino[2,3-

b]pyridin-5-ylidene)propyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 315, but replacing acetyl chloride with cyclopropylacetyl chloride.

¹H-NMR (CDCl₃) δ: 0.98-1.05 (2H, m), 1.20-1.24 (2H, m), 1.58-2.68 (5H, m), 5.40 (2H, brs), 6.23 (1H, t), 6.89 (1H, d), 7.30-7.34 (3H, m), 7.43 (2H, d), 7.59 (1H, dd), 7.86 (1H, dd), 8.00 (1H, d), 8.53 (1H, d).

MS m/z: 515 (M+1)

Example 361

4-(4-Chlorophenyl)-1-[3-(7-(3-Carboxypropionyl)-5,11-dihydro-11benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 Step 1
 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-methoxycarbonylpropionyl)benzoxepino[2,3-b]pyridin-5-ylidene)piperidin-4-ol was prepared by following the procedure of Example 315, but replacing acetyl chloride with methyl succinyl chloride.

¹H-NMR (CDCl₃) δ: 1.57-1.77 (4H, m), 1.94-2.14 (4H, m), 2.27-2.61 (6H, m), 2.61-2.73 (2H, m), 3.67 (3H, s), 4.70 (1H, t), 5.30 (2H, brs), 6.11 (1H, t), 6.83 (1H, d), 7.14 (1H, d), 7.29-7.32 (4H, m), 7.42 (2H, d), 7.58 (1H, d), 8.50 (1H, d).

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of example 48 with the product of step 1.

¹H-NMR (DMSO-d₆) δ: 1.37-1.57 (2H, m), 1.63-1.86 (2H, m), 2.13-2.37 (4H, m), 2.45-2.63 (4H, m), 3.17-3.28 (4H, m), 4.85 (1H, brs), 5.36 (2H, brs), 6.30 (1H, t), 6.91 (1H, d), 7.35 (2H, d), 7.46-7.50 (3H, m), 7.78-7.83 (2H, m), 7.95 (1H, d), 8.53 (1H, dd).

MS m/z: 547 (M+1)

Example 362

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethyl-1-hydroxy)propyl)benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by flowing the procedure of example 242, but replacing methylmagnesium bromide with ethylmagnesium bromide.

Example 363

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¹H-NMR (CDCl₃) δ: 0.79(6H, t), 1.65-2.04(9H, m), 2.35-2.66(8H, m), 5.37(2H, brs), 6.09(1H, t), 6.81(1H, d), 7.10(1H, dd), 7.26-7.51(6H, m), 7.59(1H, dd), 8.49(1H, dd).

5 MS m/z: 533 (M+1)

Example 363

4-(4-Chlorophenyl)-1-[3-(7-(1-cyano-1-methyl)ethyl)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

10 Step 1

5-(3-bromopropylidene)-7-(1-hydroxy-1-methyl)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridine was prepared by following the procedure of Example 200, but replacing the product of example 48 with the product of example 315,

15 step 1.

¹H-NMR (CDCl₃) δ: 1.58(6H, s), 2.74(2H, q), 3.47(2H, t), 5.34(2H, brs), 6.09(1H, t), 6.82(1H, d), 7.25-7.31(2H, m), 7.45(1H, d), 7.57(1H, dd), 8.52(1H, dd).

Step 2

20 To a solution of the product of step 1 (3.8 g) in dichloromethane (40 ml) was added trimethylsilyl cyanide (4.1 ml) and boron trifluoride diethyl etherate (2.5 ml) at 0 °C, and the mixture stirred at room temperature for 10 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:3) to give 5-(3-bromopropylidene)-7-(1-

cyan-1-methyl)ethyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridine (3.4 g).

¹H-NMR (CDCl₃) δ: 1.58(6H, s), 2.76(2H, m), 3.48(2H, t), 5.34(2H, brs), 6.09(1H, t), 6.87(1H, d), 7.22(1H, dd), 7.32(1H, dd), 7.42(1H, d), 7.58(1H, dd), 8.55(1H, dd).

Step 3

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 2.

10

¹H-NMR (CDCl₃) δ: 1.58(6H, s), 1.60-1.70(2H, m), 1.93-2.12(2H, m), 2.30-2.47(4H, m), 2.50-2.74(4H, m), 5.31(2H, brs), 6.15(1H, t), 6.86(1H, d), 7.19(1H, dd), 7.28-7.32(3H, m), 7.41-7.43(3H, m), 7.61(1H, d), 8.53(1H, dd).

MS m/z: 514 (M+1)

Example 364

4-(4-Chlorophenyl)-1-[3-(7-cyano-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with 5-(3-bromopropylidene)-7-cyano-5,11-dihydro[1]benzoxepino[2,3-b]pyridine.

¹H-NMR (CDCl₃) δ: 1.62-1.75(2H, m), 1.98-2.09(2H, m), 2.36-2.69(8H, m), 5.36(2H, brs), 6.19(1H, t), 6.89(1H, d), 7.29-7.62(8H, m), 8.55(1H, d).

MS m/z: 472 (M+1)

Example 365

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(tetrazol-5-yl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

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To a solution of the product of Example 364 (1.0g) in DMF (1.0ml) were added sodium azide (0.69g) and ammonium chloride (0.56g) and the mixture stirred at 100 °C for 35 hour. Water was added to the reaction mixture, and the precipitate was filtered and washed with ethanol to give the titled compound (800mg).

¹H-NMR (DMSO-d₆) δ: 1.66-1.71(2H, m), 1.91-2.01(2H, m), 2.86-3.09(8H, m), 5.33(2H, brs), 6.22(1H, t), 6.91(1H, d), 7.39-7.51(5H, m), 7.79-7.84(2H, m), 8.03(1H, d), 8.55(1H, dd).

MS m/z: 515(M+1)

¹H-NMR (DMSO-d₆) δ: 1.66-1.71(2H, m), 1.91-2.01(2H, m), 2.86-3.09(8H, m), 5.33(2H, brs), 6.22(1H, t), 6.91(1H, d), 7.39-7.51(5H, m), 7.79-7.84(2H, m), 8.03(1H, d), 8.55(1H, dd).

MS m/z: 515(M+1)

Example 366

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(hydroxymiminomethyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 357, but replacing the product of example 315, step 2 with the product of example 314.

¹H-NMR (DMSO-d₆) δ: 141-1.52(2H, m), 1.70-1.82(2H, m), 2.27-2.46(8H, m), 4.83(1H, s), 5.37(2H, brs), 6.20(1H, t), 6.83(1H, d), 7.34-7.53(7H, m), 7.76(2H, dd), MS m/z: 490(M+1)

Example 367

1-(4-Chlorophenyl)-4-[3-(5,11-dihydro-7-(1-hydroxy-1-methyl)ethyl][1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl)piperazine

The titled compound was prepared by following the procedure of example 71, but replacing the product of example 45, step 2 with the product of Example 363, step 1.

¹H-NMR (CDCl₃) δ: 1.58(6H, s), 2.31-2.63(8H, m), 3.02-

3.20(4H, m), 5.32(2H, brs), 6.12(1H, t), 6.79-6.83(3H, m), 7.17-7.31(6H, m), 7.45(1H, d), 7.58(1H, dd), 8.51(1H, dd). MS m/z: 490 (M+1)

Example 368

5 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-sulfamoyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

To the product of example 53, step 1 (5.4g) was added chlorosulfonic acid (50mL) and the mixture stirred at 0°C for 1 hour. The reaction mixture was poured to ice, and ethyl acetate was added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. To the residue were added THF (250mL) and ammonium hydroxide (30mL) and the mixture stirred at room temperature for 10 minutes. Ethyl acetate and water were added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with

magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give 5-(3-bromopropylidene)-5,11-dihydro-7-sulfamoyl[1]benzoxepino[2,3-b]pyridine (5.0g).

¹H-NMR (CDCl₃) δ: 2.70-2.75(2H, m), 3.48(2H, t), 5.39-5.49(4H, m); 6.16(1H, t), 6.88(1H, d), 7.25-7.34(2H, m),

7.53(1H, dd), 7.68(1H, dd), 7.93(1H, d), 8.53(1H, dd).

Step 2

The titled compound was prepared by following the

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procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 1.

¹H-NMR (DMSO-d₆) δ: 1.65-1.70 (3H, m), 1.98-2.07 (2H, m), 2.35-2.64 (8H, m), 4.98 (2H, brs), 5.39 (2H, brs), 6.22 (1H, t), 6.92 (1H, d) 7.26-7.43 (5H, m), 7.55-7.69 (2H, m), 7.91 (1H, d), 8.53 (1H, dd).

MS m/z: 526 (M+1)

Example 369

1-[3-(7-(2-Aminothiazol-4-yl)-5,11-

10 dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

7-bromacetyl-5-(3-bromopropylidene)-5, 11-

dihydro[1]benzoxepino[2,3-b]pyridine

15 was prepared by following the procedure of example 315, step 1, but replacing acetyl chloride with bromoacetyl chloride.

¹H-NMR (CDCl₃) δ: 2.77 (2H, m), 3.50 (2H, m), 4.40 (2H, s),

5.45 (2H, brs), 6.17 (1H, t), 6.90 (1H, d), 7.35 (1H, dd),

7.60 (1H, dd), 7.79 (1H, dd), 8.01 (1H, d), 8.57 (1H, dd).

Step 2

To a solution of the product of step 1 (1.1 g) in ethanol (11 mL) was added thiourea (193mg) at room temperature, and the mixture stirred at 70°C for 30 minutes. The

25 reaction mixture was cooled to room temperature and poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride, and dried with magnesium sulfate.

30 The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give 7-(2-aminothiazol-4-yl)-5-(3-

bromopropylidene)-5,11-dihydro[1]benzoxepino[2,3-b]pyridine (749 mg).

¹H-NMR (CDCl₃) δ: 2.74 (2H, m), 3.47 (2H, t), 5.02 (2H, brs), 5.39 (2H, brs), 6.16 (1H, t), 6.62 (1H, s), 6.85 (1H, d), 7.30 (1H, dd), 7.54-7.57 (2H, m), 7.77 (1H, d), 8.53 (1H, dd).

Step 3

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with the product of step 2.

10 ¹H-NMR (CDCl₃) δ: 1.57-1.70 (2H, m), 1.83-2.13 (2H, m), 2.30-2.46 (4H, m), 2.46-2.60 (2H, m), 2.60-2.73 (2H, m), 5.02 (2H, s), 5.37 (2H, brs), 6.20 (1H, t), 6.61 (1H, s), 6.85 (1H, d), 7.27-7.32 (3H, m), 7.42 (2H, d), 7.50-7.58 (2H, m), 7.76 (1H, d), 8.50 (1H, dd).

15 MS m/z: 545 (M+1)

17 Example 370

1-[3-(7-(3-Carboxy-1-hydroxy)propyl-5,11-

20 dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-methoxycarbonyl-1-hydroxy)propyl)[1]benzoxepino[2,3-b]pyridin-5-

25 the procedure of example 199, but replacing the product of example 138 with the product of Example 361, step 1.

¹H-NMR (CDCl₃) δ: 1.57-1.77 (4H, m), 1.94-2.14 (4H, m), 2.27-

2.61 (6H, m), 2.61-2.73 (2H, m), 3.67 (3H, s), 4.70 (1H, t),

5.30 (2H, brs), 6.11 (1H, t), 6.83 (1H, d), 7.14 (1H, d), 7.29-

30 7.32 (4H, m), 7.42 (2H, d), 7.58 (1H, d), 8.50 (1H, d).

Step 2

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The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product step 1.

¹H-NMR (DMSO-d₆) δ: 1.44-1.63 (2H, m), 1.69-1.90 (2H, m), 2.17-2.29 (2H, m), 2.29-2.82 (6H, m), 3.24-3.53 (4H, m), 4.49 (1H, t), 5.03 (1H, brs), 5.20 (2H, brs), 6.13 (1H, t), 6.76 (1H, d), 7.12 (1H, dd), 7.27 (1H, d), 7.37 (2H, d), 7.43-7.48 (3H, m), 7.76 (1H, d), 8.32 (1H, s), 8.51 (1H, dd).

MS m/z: 549 (M+1)

Example 373

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-fluoroethylamino)carbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-b]pyridin-5-ylidene)propylpiperidin-4-ol

The titled compound was prepared by following the procedure of example 368, but replacing ammonium hydroxide with dimethylamine.

¹H-NMR (CDCl₃) δ: 1.55-1.75 (3H, m), 1.96-2.07 (2H, m), 2.35-2.67 (8H, m), 2.71 (6H, s), 5.51 (2H, brs), 6.19 (1H, t), 6.92 (1H, d), 7.29-7.73 (8H, m), 8.55 (1H, dd).

MS m/z: 554 (M+1)

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(1-Carboxy-2-hydroxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

Example 374

1-[3-(7-(1-Carboxy-2-hydroxyethyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-ethoxycarboxy-2-hydroxyethyl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following

the procedure of example 199, but replacing the product of example 138 with the product of example 294.

¹H-NMR (CDCl₃) δ: 1.65-1.70 (2H, m), 2.01-2.11 (2H, m), 2.35-2.70 (8H, m), 3.76 (3H, s), 3.97-4.08 (2H, m), 4.71 (1H, t), 5.25 (1H, brs) 6.02 (1H, t) 6.70-6.91 (3H, m), 7.23-7.56 (6H, m), 8.44 (1H, dd).

Step 2

Example 371

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-

fluoroethylamino)carbonylmethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propylpiperidin-4-ol

The titled compound was prepared by following the procedure of example 134, but replacing dimethylamine hydrochloride with 2-fluoroethylamine.

¹H-NMR (CDCl₃) δ: 1.62-1.71 (3H, m), 1.98-2.10 (2H, m), 2.36-

2.71 (8H, m), 3.63 (1H, q), 3.73 (1H, q), 4.46 (1H, t), 4.49 (2H, s), 4.63 (1H, t), 5.29 (2H, brs), 6.10 (1H, t), 6.75-6.96 (4H, m), 7.28-7.44 (5H, m), 7.60 (1H, dd), 8.51 (1H, dd).

MS m/z: 566 (M+1)

Example 372

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(N-methylsulfamoyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with methylamine.

Step 2

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The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of Step 1.

¹H-NMR (DMSO-d₆) δ: 1.51-1.56 (2H, m), 1.86-1.94 (2H, m), 2.33-2.67 (8H, m), 3.65-3.82 (2H, m), 4.58 (1H, t), 5.17 (2H, brs), 6.10 (1H, t), 6.71-6.89 (3H, m), 7.34-7.47 (5H, m), 7.72 (1H, dd), 8.48 (1H, dd).

MS m/z: 551 (M+1)

Example 375

10 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ureidomethyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of example 314 (800 mg) in acetic acid (20 ml) were added urea (2 g) and trimethylsilyl chloride (0.24 ml) at room temperature, and the mixture stirred for 2 hours. Sodium borohydride was added to the reaction mixture at room temperature, and the mixture was stirred for 1 hour. The solvent was distilled off under reduced pressure, and, chloroform, 2-propanol and water were added. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol-ammonium hydroxide (100:10:1) to give the titled compound (250 mg).

¹H-NMR (CDCl₃) δ: 1.62-2.04 (5H, m), 2.35-2.69 (8H, m), 4.26 (2H, d), 4.40 (2H, s), 4.48 (1H, t), 5.32 (2H, brs), 6.12 (1H, t), 6.80 (1H, d), 7.07 (1H, dd), 7.23-7.58 (7H, m), 8.49 (1H, dd).
MS m/z: 519 (M+1)

Example 376

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

methylthio[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 44, step 2, but replacing the product of example 44, step 1 with 5-(3-bromopropylidene)-5,11-dihydro-7-methylthio[1]benzoxepino[2,3-b]pyridine.

¹H-NMR (CDCl₃) δ: 1.53-1.70 (3H, m), 1.98-2.16 (2H, m), 2.17 (3H, s), 2.34-2.70 (8H, m), 5.32 (2H, brs), 6.12 (1H, t), 6.81 (1H, d), 7.11-7.44 (7H, m), 7.57 (1H, dd), 8.50 (1H, dd).

10 MS m/z: 493 (M+1)

Example 377

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-furanon-3-yl)oxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of example 46, but replacing ethyl iodide with 3-bromotetrahydro-2-furanone.

¹H-NMR (CDCl₃) δ: 1.1-1.65-1.70 (2H, m), 1.97-2.13 (2H, m), 2.25-2.73 (10H, m), 4.25-4.53 (2H, m), 4.82 (1H, t), 5.27 (2H, brs), 6.09 (1H, t), 6.73-6.91 (2H, m), 7.03 (1H, d), 7.22-7.59 (6H, m), 8.43 (1H, dd).
MS m/z: 547 (M+1)

Example 378

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(N-methoxycarbonylmethylsulfonyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with glycine methyl ester hydrochloride.

¹H-NMR (CDCl₃) δ: 1.66-1.74 (3H, m), 1.97-2.15 (2H, m), 2.37-2.80 (8H, m), 3.63 (3H, s), 3.78 (2H, s) 5.40 (2H, brs),

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6.22 (1H, t), 6.92 (1H, d), 7.28-7.45 (5H, m), 7.62 (2H, dd),
 7.83 (1H, d), 8.53 (1H, dd).
 MS m/z: 598 (M+1)

Example 379

5 1-[3-(7-(N-Carboxymethylsulfamoyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of example 133, but replacing the product of example 48 with the product of Example 378.

¹H-NMR (DMSO-d₆) δ: 1.60-1.65 (2H, m), 2.16-2.25 (2H, m), 2.43-3.03 (8H, m), 3.45 (2H, s), 5.33 (2H, brs), 6.39 (1H, t), 6.94 (1H, d), 7.41-7.57 (6H, m), 7.83 (1H, dd), 8.00 (1H, d), 8.54 (1H, dd).

Example 380

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-furanon-5-yl)[1]benzoxepino[2,3-b]pyridin-5-

yldene)propyl]piperidin-4-ol

The titled compound was prepared by following the

procedure of example 249, step 1 with the product of Example 370, step 1.

¹H-NMR (CDCl₃) δ: 1.45-1.78 (4H, m), 1.93-2.12 (2H, m), 2.30-2.50 (4H, m), 2.50-2.78 (6H, m), 5.33 (2H, brs), 5.46 (1H, t), 6.12 (1H, t), 6.86 (1H, d), 7.09 (1H, dd), 7.27-7.32 (4H, m), 7.42 (2H, d), 7.58 (1H, dd), 8.51 (1H, dd).
 MS m/z: 531 (M+1)

Example 381

1-[3-(7-amino-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

30 ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of the produce of example 293 (3.7g) in ethanol (130ml) was added 5N sodium hydroxide solution (100ml) and the mixture stirred at 90°C for 1 hour. The reaction mixture was distilled off under reduced pressure.

5 The residue was dissolved with water and neutralized with 1N hydrochloric acid. Ethyl acetate was added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate to give the titled compound (3.0g).

¹H-NMR (CDCl₃) δ: 1.62-1.72 (2H, m), 1.96-2.08 (2H, m), 2.27-2.72 (8H, m), 3.48 (2H, brs), 5.23 (2H, brs), 6.01 (1H, t), 6.49-6.73 (3H, m), 7.18-7.59 (6H, m), 8.49 (1H, dd).
 MS m/z: 462 (M+1)

Example 382

15 1-[3-(7-(2-Carboxyphenyl)-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-5-

ol

Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-formylphenyl)[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidin-4-ol was prepared by following the similar procedure of example 170, but replacing allyltributyltin with 2-formylphenylboronic acid.

¹H-NMR (CDCl₃) δ: 1.65-1.91 (3H, m), 1.99-2.04 (2H, m), 2.37-2.65 (8H, m), 5.39 (2H, brs), 6.15 (1H, t), 6.95 (1H, d), 7.19-7.65 (10H, m), 7.97-8.05 (2H, m), 8.52 (1H, dd), 10.03 (1H, s).

Step 2

To a solution of the product of step 1 (270mg) in acetic acid (2.2 ml) and water (0.5ml) were added amidosulfuric acid (67mg) and sodium chlorite (68mg) in water (0.1ml), and the mixture was stirred at room temperature for 15

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minutes. The reaction mixture was distilled off under reduced pressure into half volume. The residue was neutralized with 1N sodium hydroxide. The precipitation was filtered and washed with water to give the titled compound (80mg).

¹H-NMR (DMSO-d₆) δ: 1.41-1.57(2H, m), 1.74-1.92(2H, m),

2.21-2.58(8H, m), 5.32(2H, brs), 6.20(1H, t), 6.82(1H, d), 7.15(1H, dd), 7.31-7.78(11H, m), 8.52(1H, dd). MS m/z: 567(M+1)

10 Example 383

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(N-(2,2,2-trifluoroethyl)sulfamoyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 368, but replacing ammonium hydroxide with 2,2,2-trifluoroethylamine hydrochloride.

¹H-NMR (CDCl₃) δ: 1.64-1.77(2H, m), 1.97-2.18(2H, m), 2.35-2.80(8H, m), 3.63(2H, q), 5.41(2H, brs), 6.21(1H, t), 6.91(1H, d), 7.22-7.65(7H, m), 7.84(1H, d), 8.57(1H, dd). MS m/z: 608(M+1)

10

The titled compound was prepared by following the procedure of Example 293, but replacing ethanol with phenol.

¹H-NMR (CDCl₃) δ: 1.62-1.68(2H, m), 1.96-2.08(2H, m), 2.35-2.65(8H, m), 5.28(2H, brs), 6.10(1H, t), 6.78(1H, m), 7.08-7.40(6H, m), 7.52(1H, dd), 7.62(1H, s), 8.44(1H, dd). MS m/z: 582(M+1)

Step 2

To a solution of the product of Step 1 (300mg) in DMF (3mL) was added ammonium hydroxide (1.5mL) and the mixture was stirred at room temperature for 2 hours. Ethyl acetate and water were added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with (chloroform : methanol = 10 : 1) to give the titled compound (140mg).

¹H-NMR (DMSO-d₆) δ: 1.45-1.50(2H, m), 1.72-1.88(2H, m), 2.28-2.51(8H, m), 4.82(1H, s), 5.19(1H, brs), 5.74(2H, brs), 6.09(1H, t), 6.69(1H, d), 7.12(1H, dd), 7.32-7.48(6H, m), 7.74(1H, dd), 8.37(1H, s), 8.50(1H, dd). MS m/z: 505(M+1)

MS m/z: 525(M+1)
Example 385
4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ureido[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 Step 1

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-phenoxy carbonylamino[1]benzoxepinol[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

10

The titled compound was prepared by following the procedure of Example 293, but replacing ethanol with phenol.

¹H-NMR (CDCl₃) δ: 1.62-1.68(2H, m), 1.96-2.08(2H, m), 2.35-2.65(8H, m), 5.28(2H, brs), 6.10(1H, t), 6.78(1H, m), 7.08-7.40(6H, m), 7.52(1H, dd), 7.62(1H, s), 8.44(1H, dd). MS m/z: 582(M+1)

Step 2

To a solution of the product of Step 1 (300mg) in DMF (3mL) was added ammonium hydroxide (1.5mL) and the mixture was stirred at room temperature for 2 hours. Ethyl acetate and water were added to the mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with (chloroform : methanol = 10 : 1) to give the titled compound (140mg).

¹H-NMR (DMSO-d₆) δ: 1.45-1.50(2H, m), 1.72-1.88(2H, m), 2.28-2.51(8H, m), 4.82(1H, s), 5.19(1H, brs), 5.74(2H, brs), 6.09(1H, t), 6.69(1H, d), 7.12(1H, dd), 7.32-7.48(6H, m), 7.74(1H, dd), 8.37(1H, s), 8.50(1H, dd). MS m/z: 505(M+1)

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Example 386

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-morpholinocarbonylamino[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of Example 385, step 2, but replacing ammonium hydroxide with morpholine.

¹H-NMR (CDCl₃) δ: 1.62-1.67(2H, m), 1.95-2.16(2H, m), 2.28-2.64(8H, m), 3.41(4H, t), 3.69(4H, t), 5.26(2H, brs), 6.08(1H, t), 6.69-6.76(2H, m), 6.98(1H, dd), 7.21-7.51(7H, m), 8.42(1H, dd).

MS m/z: 575 (M+1)

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

¹H-NMR (DMSO-d₆) δ: 1.50-1.55(2H, m), 1.87-1.99(2H, m), 2.34-2.61(11H, m), 5.29(2H, brs), 6.12(1H, s), 6.31(1H, t), 6.83(1H, d), 7.35-7.49(7H, m), 7.76(1H, dd), 8.52(1H, dd).

MS m/z: 530 (M+1)

Example 387

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-(2-ethoxy)carbonylethyl)ureido[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

procedure of Example 385, step 2, but replacing ammonium hydroxide with beta-alanine ethyl ester hydrochloride.

¹H-NMR (CDCl₃) δ: 1.18-1.39(3H, t), 1.62-1.66(2H, m), 1.92-2.01(2H, m), 2.21-2.62(10H, m), 3.47-3.50(2H, m), 4.08(2H, q), 5.22(2H, brs), 5.98-6.03(2H, m), 6.68-6.92(2H, m), 7.15-7.42(7H, m), 7.62(1H, s), 8.36(1H, dd).

MS m/z: 605 (M+1)

Step 2

The titled compound was prepared by following the procedure of Example 385, step 2, but replacing ammonium hydroxide with beta-alanine ethyl ester hydrochloride.

¹H-NMR (CDCl₃) δ: 1.18-1.39(3H, t), 1.62-1.66(2H, m), 1.92-2.01(2H, m), 2.21-2.62(10H, m), 3.47-3.50(2H, m), 4.08(2H, q), 5.22(2H, brs), 5.98-6.03(2H, m), 6.68-6.92(2H, m), 7.15-7.42(7H, m), 7.62(1H, s), 8.36(1H, dd).

MS m/z: 605 (M+1)

Example 389

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-oxalo[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

20 The titled compound was prepared by following the procedure of Example 361, but replacing methyl succinyl chloride with methyl oxalyl chloride.

¹H-NMR (DMSO-d₆) δ: 1.66-1.86(2H, m), 2.08-2.34(2H, m), 2.46-2.77(2H, m), 3.00-3.68(6H, m), 5.10(2H, brs), 5.53(1H, s), 6.15(1H, t), 6.89(1H, d), 7.34-7.49(5H, m), 7.68(1H, dd), 7.75(1H, dd), 7.87(1H, d), 8.53(1H, dd).

MS m/z: 519 (M+1)

Example 390

1-[3-(7-(3-(2-Carboxy-1-methyl)ethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

30 4-(4-Chlorophenyl)-1-[3-(7-(2-ethoxycarbonyl-5,11-methyl)ethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

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(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of Example 387.

¹H-NMR (DMSO-d₆) δ: 1.45-1.55(2H, m), 1.72-1.85(2H, m), 2.32-2.49(10H, m), 3.29(2H, q), 4.88(1H, s), 5.19(2H, brs), 6.06-6.14(2H, m), 6.69(1H, d), 7.07(1H, dd), 7.33-7.48(6H, m), 7.73(1H, dd), 8.43(1H, s), 8.49(1H, dd). MS m/z: 577(M+1)

10 Example 391

1-[3-(7-(3-(2-Hydroxyethyl)ureido-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 385, step 2, but replacing ammonium hydroxide with 2-aminoethanol.

¹H-NMR (DMSO-d₆) δ: 1.45-1.51(2H, m), 1.72-1.84(2H, m), 2.24-2.51(8H, m), 3.11-3.46(4H, m), 4.71(1H, t), 4.83(1H, s), 5.19(2H, brs), 6.08(1H, t), 6.69(1H, d), 7.08(1H, dd), 7.33-7.48(6H, m), 7.73(1H, dd), 8.41(1H, s), 8.50(1H, dd). MS m/z: 549(M+1)

Example 392

1-[3-(5,11-Dihydro-7-(1-hydroxy-1-methyl)ethyl][1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]-4-(2-keto-1-imidazolinyl)piperidine

The titled compound was prepared by following the procedure of Example 67, but replacing the product of Example 45, step 2 with the product of Example 363, step 1.

¹H-NMR (CDCl₃) δ: 1.59(6H, s), 1.71-1.87(2H, m), 2.01-2.18(2H, m), 2.20-2.61(6H, m), 2.86-3.00(2H, m), 4.32(1H,

m), 5.35(2H, brs), 6.15(1H, t), 6.84(1H, d), 7.02-7.07(3H, m), 7.24-7.31(3H, m), 7.47(1H, d), 7.60(1H, dd), 8.51(1H, dd), 8.97(1H, s). MS m/z: 511(M+1)

5 Example 393

4-(4-Chlorophenyl)-1-[3-(7-(E)-(2-ethoxycarboxy-2-methyl)ethenyl]-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl)piperidin-4-ol

To a solution of sodium hydride (60% in oil, 100 mg) in THF (6 mL) were added triethyl 2-phosphonopropionate (0.3 mL) and the product of Example 314 (300 mg) at 0°C, and the mixture was stirred at room temperature for 30 minutes. Water and ethyl acetate were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (30:1) to give the titled compound (310 mg).

¹H-NMR (CDCl₃) δ: 1.34(3H, t), 1.58-1.71(3H, m), 1.98-2.15(5H, m), 2.37-2.70(8H, m), 2.27(2H, q), 5.37(2H, brs), 6.14(1H, t), 6.86(1H, d), 7.25-7.44(7H, m) 7.58-7.63(2H, m), 8.52(1H, dd). MS m/z: 559(M+1)

Example 394

25 1-[3-(7-(E)-(2-Carboxy-2-methyl)ethenyl]-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

¹H-NMR (CDCl₃) δ: 1.62-1.67(2H, m), 1.91-2.05(5H, m),

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2.50-2.94(8H, m), 5.28(2H, brs), 6.23(1H, t), 6.87(1H, d),
 7.34-7.55(8H, m), 7.79(1H, dd), 8.54(1H, dd).
 MS m/z: 531(M+1)

Example 395

5 1-[3-(7-(5-Carboxy-1-pentyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(5-ethoxycarbonyl-1-pentyl)oxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidin-4-ol was prepared by following the procedure of Example 46, but replacing ethyl iodide with ethyl 6-bromohexanoate.

¹H-NMR (CDCl₃) δ: 1.21(3H, t), 1.42-1.79(8H, m), 1.98-2.10(3H, m), 2.35-2.59(10H, m), 3.51-3.53(2H, m), 4.00(2H, q), 5.23(2H, brs), 6.00(1H, t), 6.68-6.81(3H, m), 7.24-7.56(6H, m), 8.16(1H, dd).

Step 2

The titled compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

Example 397

20 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(thiazoline-2,4-dione-5-ylidene)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 314 (590 mg) in ethanol (6 mL) were added 2,4-thiazolidinedione (440 mg) and piperidine (0.36 mL), and the mixture was heated to reflux for 3 hours. The solvent was distilled off under reduced pressure, and, chloroform, 2-propanol and water were added. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (5:1) to give the titled compound (510 mg).

Example 396

1-[3-(7-(1-(2-Carboxy)ethyl)aminocarbonyl-1-methyl)ethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(1-(2-

ethoxycarbonyl)ethyl)aminocarbonyl-1-methyl)ethoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol was prepared by following the procedure of Example 176, but replacing dimethylamine hydrochloride with beta-alanine ethyl ester hydrochloride. ¹H-NMR (CDCl₃) δ: 1.42(3H, s), 1.62-1.67(2H, m), 1.95-2.10(3H, m), 2.35-2.59(10H, m), 3.51-3.53(2H, m), 4.00(2H, q), 5.23(2H, brs), 6.00(1H, t), 6.68-6.81(3H, m), 7.24-7.56(6H, m), 8.16(1H, dd).

Step 2

The title compound was prepared by following the procedure of Example 133, but replacing the product of Example 48 with the product of step 1.

¹H-NMR (DMSO-d₆) δ: 1.37(6H, s), 1.41-1.52(2H, m), 1.79-

15 1.87(2H, m), 2.28-2.41(10H, m), 3.33(2H, q), 5.21(2H, brs), 6.12(1H, t), 6.70-6.87(3H, m), 7.34-7.48(5H, m), 7.74(1H, dd), 8.08(1H, t), 8.50(1H, dd).

MS m/z: 620(M+1)

Example 397

20 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(thiazoline-2,4-dione-5-ylidene)methyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 314 (590 mg) in ethanol (6 mL) were added 2,4-thiazolidinedione (440 mg) and piperidine (0.36 mL), and the mixture was heated to reflux for 3 hours. The solvent was distilled off under reduced pressure, and, chloroform, 2-propanol and water were added. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (5:1) to give the titled compound (510 mg).

Step 1

4-(4-Chlorophenyl)-1-[3-(7-(1-(2-

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¹H-NMR (DMSO-d₆) δ: 1.61-1.66 (2H, m), 1.97-2.12 (2H, m), 2.79-2.99 (8H, m), 5.21 (2H, brs), 6.25 (1H, t), 6.90 (1H, d), 7.34-7.52 (7H, m), 7.81 (1H, dd), 8.54 (1H, dd).
MS m/z: 574 (M+1)

5 Example 398

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methanesulfonamido[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 402, but replacing trifluoromethanesulfonic acid anhydride with methanesulfonyl chloride.

¹H-NMR (CDCl₃) δ: 1.64-1.69 (2H, m), 1.89-2.05 (2H, m), 2.24-

2.77 (8H, m), 2.95 (3H, s), 5.29 (2H, brs), 6.10 (1H, t), 6.84 (1H, d), 7.06 (1H, dd), 7.18-7.40 (6H, m), 7.56 (1H, dd), 8.42 (1H, dd).

MS m/z: 540 (M+1)

Example 401

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-propylureido)sulfonyl[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 399, but replacing phenyl isocyanate with propyl isocyanate.

¹H-NMR (DMSO-d₆) δ: 0.74 (3H, t), 1.25-1.53 (4H, m), 1.81-1.91 (2H, m), 2.33-2.59 (10H, m), 2.89 (2H, q), 4.92 (1H, s), 5.35 (2H, brs), 6.20 (1H, t), 6.44 (1H, brs), 6.96 (1H, d), 7.34-7.51 (5H, m), 7.64 (1H, dd), 7.78-7.85 (2H, m), 8.54 (1H, dd).

Example 402

¹H-NMR (DMSO-d₆) δ: 1.65-1.69 (2H, m), 1.95-2.05 (2H, m), 2.89-3.06 (8H, m), 5.31 (2H, brs), 6.14 (1H, t), 6.74-6.85 (2H, m), 7.08-7.12 (2H, m), 7.37-7.64 (8H, m), 7.80-7.84 (2H, m), 8.44 (1H, s), 8.54 (1H, dd).
MS m/z: 645 (M+1)

Example 400
4-(4-Chlorophenyl)-1-[3-(7-(3-cyclohexylureido)sulfonyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 399, but replacing phenyl isocyanate with cyclohexyl isocyanate.

¹H-NMR (DMSO-d₆) δ: 1.07-1.81 (14H, m), 2.23-2.58 (8H, m), 3.22-3.35 (1H, m), 4.91 (1H, s), 5.38 (2H, brs), 6.17-6.29 (2H, m), 6.96 (1H, d), 7.34-7.51 (5H, m), 7.62-7.84 (3H, m), 8.53 (1H, dd).
MS m/z: 651 (M+1)

30 The title compound was prepared by following the procedure

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of Example 169, but replacing the product of Example 44, step 2 with the product of Example 381.

¹H-NMR (DMSO-d₆) δ: 1.75-1.80(2H, m), 2.02-2.07(2H, m), 2.49-2.54(2H, m), 3.10-3.40(6H, m), 5.15(2H, brs), 5.52(1H, s), 5.97(1H, t), 6.58(1H, d), 6.80(1H, dd), 6.96(1H, d), 7.43-7.47(5H, m), 7.78(1H, dd), 8.51(1H, dd). MS m/z: 593 (M+1)

Example 403

1-[3-(7-(3-carboxy)propyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Step 1

To a solution of the product of Example 361, step 1 (820 mg) in TFA (8.0 mL) was added triethyl silane (0.92 mL) at 0°C, and the mixture stirred at room temperature for 4 hour. The solvent was distilled off under reduced pressure. The residue was poured into saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(3-methoxycarbonyl)propyl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]propyl-5,11-dihydro-7-(3-

20 methoxycarbonyl)propyl][1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]propyl-5,11-dihydro-7-(3-methoxycarbonyl)propyl-1-[3-(5,11-dihydro-7-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 407 (1.7 g) in DMF (20 mL) was added 2-ethylhexyl chloroformate (0.62 mL) and the mixture was stirred at 0°C for 1 hour. Chloroform and water were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (30:1) and dissolved in xylene (50 mL). The solution was 30 heated to reflux for 4 hours. The solvent was distilled off under reduced pressure. The residue was reslurried

Step 2

MS m/z: 533 (M+1)

Example 404

1-[3-(7-Benzoylsulfamoyl-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]-4-(4-chlorophenyl)piperidin-4-ol

The titled compound was prepared by following the procedure of Example 399, but replacing phenyl isocyanate with benzoyl chloride.

MS m/z: 630 (M+1)

Example 405

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,5-dihydro-5-

20 oxo-4H-1,2,4-oxadiazol-3-yl)methoxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 407 (1.7 g) in DMF (20 mL) was added 2-ethylhexyl chloroformate (0.62 mL) and the mixture was stirred at 0°C for 1 hour. Chloroform and water were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (30:1) and dissolved in xylene (50 mL). The solution was 30 heated to reflux for 4 hours. The solvent was distilled off under reduced pressure. The residue was reslurried

Step 2

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with ethanol to the titled compound (490 mg).

¹H-NMR (DMSO-d₆) δ: 1.60-1.65(2H, m), 1.91-1.99(2H, m), 2.41-2.52(2H, m), 2.70-2.89(6H, m), 4.90(2H, s), 5.19(2H, brs), 6.16(1H, t), 6.75-7.05(3H, m), 7.37-7.48(5H, m), 7.75(1H, dd), 8.52(1H, dd).

MS m/z: 561(M+1)

Example 406

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the procedure of Example 405, but replacing the product of Example 407 with the product of Example 408.

Example 407

¹H-NMR (DMSO-d₆) δ: 1.58-1.63(2H, m), 1.87-1.96(2H, m), 2.40-2.51(2H, m), 2.63-2.85(6H, m), 5.14(2H, brs), 6.23(1H, t), 6.92(1H, d), 7.36-7.52(6H, m), 7.77-7.81(2H, m), 8.54(1H, dd).

MS m/z: 531(M+1)

Example 407

20 4-(4-Chlorophenyl)-1-[3-(7-hydroxyamidinomethoxy-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-

ylidene)propyl]piperidin-4-ol

The titled compound was prepared by following the

procedure of Example 355, but replacing the product of

Example 313 with the product of Example 49.

¹H-NMR (DMSO-d₆) δ: 1.45-1.50(2H, m), 1.73-1.81(2H, m), 2.28-2.51(8H, m), 4.83(1H, s), 5.79(2H, brs), 6.25(1H, t), 6.81(1H, d), 7.33-7.49(6H, m), 7.63-7.76(2H, m), 8.51(1H, dd), 9.48(1H, s).

MS m/z: 505(M+1)

Example 409

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)methyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

To a solution of the product of Example 407 (700 mg) in THF (20 mL) were added pyridine (0.21 mL) and thionyl chloride (0.1 mL) at 0°C, and the mixture was stirred at

20 0°C for 1 hour and the mixture was stirred at room temperature for 30 minutes. Water, chloroform and 2-propanol were added to the reaction mixture. The organic layer was extracted and the solvent was distilled off under reduced pressure. The residue was purified by

25 silica gel chromatography eluting with chloroform-methanol (5:1) to give the titled compound (170 mg).

MS m/z: 581(M+1)

Example 410

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)methyloxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

MS m/z: 535(M+1)

Example 408
4-(4-Chlorophenyl)-1-[3-(7-hydroxyamidino-5,11-dihydro[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidin-4-ol

5 The titled compound was prepared by following the procedure of Example 355, but replacing the product of Example 313 with the product of Example 364.

¹H-NMR (DMSO-d₆) δ: 1.45-1.50(2H, m), 1.73-1.81(2H, m), 2.28-2.51(8H, m), 4.83(1H, s), 5.79(2H, brs), 6.25(1H, t), 6.81(1H, d), 7.33-7.49(6H, m), 7.63-7.76(2H, m), 8.51(1H, dd), 9.48(1H, s).

MS m/z: 505(M+1)

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To a solution of the product of Example 407 (700 mg) in THF (20 ml) was added thiocarbonyldimidazole (280 mg) and the mixture was stirred at room temperature for 30 minutes. Water and ethyl acetate were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. To the residue were added THF (50 ml) and boron trifluoride diethyl etherate (0.8 ml), and the mixture was stirred at room temperature for 1 hour. Chloroform, 2-propanol and water were added to the reaction mixture. The organic layer was extracted, and the solvent was distilled off under reduced pressure. The residue was reslurried with acetone to the titled compound (180 mg).

MS m/z: 577 (M+1)

¹H-NMR (CDCl₃) δ: 1.26 (3H, t), 1.67-1.85 (2H, m), 1.93-2.13 (2H, m), 2.28-2.47 (4H, m), 2.47-2.60 (2H, m), 2.60-2.76 (2H, m), 3.94 (2H, s), 4.21 (2H, q), 5.60 (2H, brs), 6.22 (1H, t), 6.88 (1H, d), 7.29-7.34 (3H, m), 7.43 (2H, d), 7.59 (1H, d), 7.71 (1H, dd), 7.97 (1H, d), 8.53 (1H, d).

10 ¹H-NMR (CDCl₃) δ: 1.26 (3H, t), 1.67-1.85 (2H, m), 1.93-2.13 (2H, m), 2.28-2.47 (4H, m), 2.47-2.60 (2H, m), 2.60-2.76 (2H, m), 3.94 (2H, s), 4.21 (2H, q), 5.60 (2H, brs), 6.22 (1H, t), 6.88 (1H, d), 7.29-7.34 (3H, m), 7.43 (2H, d), 7.59 (1H, d), 7.71 (1H, dd), 7.97 (1H, d), 8.53 (1H, d).

15 Example 411
To a solution of the product of Example 407 (700 mg) in THF (20 ml) was added LDA (0.51 mol/L THF-hexane solution, 3.0 ml) at -78°C, and the mixture stirred at room temperature for 20 minutes. The reaction mixture was cooled to -78°C again, and added ethyl cyanoformate (76 μl), stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and aqueous sodium chloride were added to the mixture, and the aqueous layer was washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with chloroform-methanol (10:1) to give the titled compound (280 mg).

20 ¹H-NMR (DMSO) δ: 1.64-1.69 (2H, m), 1.74-1.85 (2H, m), 2.27-2.52 (8H, m), 4.81 (1H, s), 5.16 (2H, brs), 6.08 (1H, t), 6.62-6.71 (3H, m), 7.12 (2H, t), 7.40-7.51 (3H, m), 7.72 (1H, dd), 8.48 (1H, dd), 9.09 (1H, s). ESI-MS m/z: 447 (M + 1).

25 Example 412
To a solution of the product of Example 407 (700 mg) in

2.13 (2H, m), 2.28-2.47 (4H, m), 2.47-2.60 (2H, m), 2.60-2.76 (2H, m), 3.94 (2H, s), 4.21 (2H, q), 5.60 (2H, brs), 6.22 (1H, t), 6.88 (1H, d), 7.29-7.34 (3H, m), 7.43 (2H, d), 7.59 (1H, d), 7.71 (1H, dd), 7.97 (1H, d), 8.53 (1H, d).

MS m/z: 561 (M+1)

Example 412:

4-(4-fluorophenyl)-1-[3-(5,11-dihydro-7-hydroxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine-4-ol

10 To a solution of 5-(3-bromopropylidene)-5,11-dihydro-7-hydroxy-[1]benzoxepino[2,3-b]pyridin-5-ylidene) (10 ml) was added 4-(4-Fluorophenyl)-4-hydroxypiperidine (1.02 g) and triethylamine (835 μM). The solution was

15 stirred at room temperature for 23 hours. The reaction was quenched with water, extracted with ethyl acetate, and evaporated in vacuo. The residue was purified by silica gel chromatography (87:10:3 ethyl acetate: methanol: triethylamine) to yield 0.9 g (39%) of the title compound.

20 ¹H-NMR (DMSO) δ: 1.64-1.69 (2H, m), 1.74-1.85 (2H, m), 2.27-2.52 (8H, m), 4.81 (1H, s), 5.16 (2H, brs), 6.08 (1H, t), 6.62-6.71 (3H, m), 7.12 (2H, t), 7.40-7.51 (3H, m), 7.72 (1H, dd), 8.48 (1H, dd), 9.09 (1H, s). ESI-MS m/z: 447 (M + 1).

25 Example 413
4-(4-fluorophenyl)-1-[3-(5,11-dihydro-7-carboxy[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine-4-ol

30 The titled compound was prepared by following the procedure of example 118, but replacing the compound of Example 169 with the triflate derived from compound 412.

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¹H-NMR (MeOD) δ: 1.78-1.85 (2H, m), 2.25-2.40 (2H, m), 2.57-2.70 (2H, m), 3.06-3.35 (7H, m), 5.06-5.81 (2H, brs), 6.23 (1H, t), 6.77 (1H, d), 7.00-7.11 (2H, m), 7.37-7.56 (3H, m), 7.65-7.80 (2H, m), 8.01 (1H, d), 8.48 (1H, dd).

5 MS m/z: 475

Example 414

4-(4-fluorophenyl)-1-[3-(5,11-dihydro-7-(1-hydroxy-1-methylethyl)-[1]benzoxepino[2,3-b]pyridin-5-ylidene)propyl]piperidine-4-ol

10 The titled compound was prepared by following the procedure of Example 27, but starting with the methyl ester of the compound of Example 413.

¹H-NMR (CDCl₃) δ: 1.57-2.14 (12H, m), 2.34-2.45 (4H, m), 2.50-2.61 (2H, m), 2.63-2.78 (2H, m), 5.22-5.43 (2H, brs), 6.14 (1H, t), 6.95-7.10 (2H, m), 7.25-7.35 (2H, m), 7.40-7.60 (4H, m), 8.50 (1H, dd).

MS m/z: 489

Example 415:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-diethylcarbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 316, but replacing dimethylamine with diethylamine.

25 ¹H-NMR (CDCl₃) δ: 1.18-1.30 (6H, m), 1.65 (2H, d), 1.80 (1H, s), 2.05 (2H, dt), 2.30-2.45 (4H, m), 2.50 (2H, t), 2.60-2.70 (2H, m), 3.35-3.50 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 6.90 (1H, dd), 7.10 (1H, dd), 7.23-7.35 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.50 (1H, dd).

30 MS m/z: 563

Example 416:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-phenylsulfonylcarbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

To a solution of the compound of Example 44 (0.511 g, 1.1 mmol) in dry THF (20 mL) was added sodium hydride (60% in mineral oil, 48 mg, 1.2 mmol), and the slurry heated at 40°C under argon with stirring for 20 minutes.

10 Phenylsulfonylisocyanate (160 μL, 1.2 mmol) was added and the mixture was stirred for 14 hours. The solvent was then removed by rotary evaporation to give the crude product. The solid material was washed twice with 20 mL CH₂Cl₂, and then twice with 20 mL MeOH: CH₂Cl₂ (1:1) to give the title compound (274 mg).

15 MS m/z: 647

Example 417:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxycarbonyl-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

20 To a solution of the compound of Example 44 (0.214 g, 0.46 mmol) in dry THF (5mL) was added sodium hydride (60% in mineral oil, 28 mg, 0.7 mmol), and the slurry heated at 50°C under argon with stirring for 20 minutes. Methyl isocyanatoformate (56 μL, 0.7 mmol) was added and the mixture was stirred for 14 hours. The solvent was then removed by rotary evaporation to give the crude product. The residue was purified by silica gel chromatography eluting with a dichloromethane/2.0 M ammonia in methanol gradient (0 to 4% MeOH over 1 hour) to give the title compound (102 mg).

25 ¹H-NMR (CDCl₃) δ: 1.60-1.65 (2H, m), 1.80 (1H, s), 2.05 (2H, dt), 2.30-2.45 (4H, m), 2.50 (2H, t), 2.60-2.70 (2H, m), 3.35-3.50 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 6.90 (1H, dd), 7.10 (1H, dd), 7.23-7.35 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.50 (1H, dd).

30 ¹H-NMR (CDCl₃) δ: 1.60-1.65 (2H, m), 1.80 (1H, s), 2.05 (2H, dt), 2.30-2.45 (4H, m), 2.50 (2H, t), 2.60-2.70 (2H,

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m), 3.35 (3H, s), 5.30 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 6.90 (1H, dd), 7.10 (1H, dd), 7.23-7.35 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.50 (1H, dd).
MS m/z: 565

5 Example 418:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(R-3-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

10 Step 1:

R-ethyl nipecotate-L-tartrate (1.53 g) was freebased with aqueous sodium hydroxide and ethyl acetate. The organic layers were evaporated, and the resulting amine was

15 redissolved in THF (10 mL) and treated with carbonyl-diimidazole (0.81 g). The resulting solution was stirred at room temperature for 23 hours, concentrated in vacuo, and redissolved in acetonitrile (5 mL). This solution was treated with methyl iodide (0.347 mL) and stirred for 18 hours at room temperature.

20 Step 2:
The compound of Example 44 (0.7 g) was suspended in THF (25 mL) and treated with sodium hydride (0.036 g) and stirred at room temperature for one hour. The resulting

anion was added to the imidazolium salt prepared in Step 25 1, and the solution was heated to reflux for 18 hr. The crude material was then loaded on silica gel and purified by silica gel chromatography (87:10:3 ethyl acetate:methanol:triethylamine) to yield 0.278 g (64%) of the title compound.

30 $^1\text{H-NMR}$ (DMSO) δ : 1.11-1.21 (3H, m), 1.45-2.0 (8H, m), 2.15-2.40 (6H, m), 3.05-3.15 (2H, m), 3.31 (2H, m), 3.95-4.15 (3H, m), 5.31 (2H, brs), 6.14 (1H, t), 6.78 (1H, d),

Example 419:

5 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(R-3-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The compound of Example 418 (0.195 g) was dissolved in THF (1 mL) and treated with aqueous lithium hydroxide (0.0084 g) and stirred at room temperature for 18 hours. The resulting solution was concentrated in vacuo, and the residue was purified by chromatography on a reverse-phase solid-phase-extraction column, eluting with water-acetonitrile, 0.1% formic acid, to yield 0.153 g (77%) of the title compound.

$^1\text{H-NMR}$ (DMSO) δ : 1.55-2.25 (8H, m), 2.30-2.80 (10H, m), 3.22 (1H, m), 4.15-4.35 (2H, m), 5.41 (2H, brs), 6.35 (1H, t), 6.98 (1H, d), 7.13 (1H, dd), 7.25 (1H, d), 7.54 (2H, d), 7.64 (3H, m), 7.90 (1H, dd), 8.50 (1H, s), 8.70 (1H, dd).
ESI-MS m/z: 618 ($M + 1$).

Example 420:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-ethoxycarbonyl-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 418, but replacing R-ethyl nipecotate-L-tartrate with ethyl isonipecotate.

30 $^1\text{H-NMR}$ (CDCl₃) δ : 1.25 (3H, t), 1.60-1.80 (4H, m), 1.90-2.05 (4H, m), 2.25-2.65 (10H, m), 2.90-3.15 (2H, m), 4.05-

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4.25 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.75-6.90 (2H, m), 7.05 (1H, d), 7.20-7.40 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.45 (1H, dd).

MS m/z: 647

5 Example 421:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(4-carboxy-piperidine-1-yl)-carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

A solution of the compound of Example 420 (91 mg, 0.14 mmol) in MeOH (5 mL) was treated with a 0.4 M solution of lithium hydroxide (5 mL, 2 mmol) and stirred for 3 hours. After addition of 5 mL of 0.4 N HCl, the solvent was removed under reduced pressure to give the crude product. The residue was purified using silica gel chromatography eluting with a dichloromethane:methanol gradient (0 to 50% MeOH over 1 hour) to give the title compound (48 mg).

¹H-NMR (MeOD) δ: 1.60-1.65 (2H, m) 2.10-2.70 (10H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.80-6.90 (2H, m), 7.20-7.50 (6H, m), 7.62 (1H, dd), 8.48 (1H, dd).

MS m/z: 619

Example 422:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(S-3-ethoxycarbonyl-piperidine-1-yl)- carbamoyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 418, but replacing R-ethyl nipecotate-L-tartrate with ethyl (S)-nipecotate-D-tartrate.

30 tartrate.

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¹H-NMR (CDCl₃) δ: 1.25 (3H, t), 1.30-1.70 (5H, m), 1.94-2.05 (3H, m), 2.25-2.65 (11H, m), 3.05-3.15 (1H, m), 4.05-4.25 (4H, m), 5.30 (2H, brs), 6.15 (1H, t), 6.75-6.90 (2H, m), 7.05 (1H, d), 7.20-7.40 (3H, m), 7.40 (2H, d), 7.56 (1H, dd), 8.45 (1H, dd).

MS m/z: 647

Example 423:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-ethoxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The compound of Example 169 (0.166 g) was dissolved in DMF (1 mL) and treated with palladium (II) acetate (0.007 g), 1,3-bis(diphenylphosphino)propane (0.012 g), triethylamine (0.1 mL) and ethanol (1 mL), and stirred at 60°C for 18 hours under a CO balloon. The resulting solution was quenched with water, extracted with ethyl acetate, concentrated in vacuo, and purified by silica gel chromatography (87:10:3 ethyl acetate:methanol:triethylamine). The residue was further purified by chromatography on a reverse-phase solid-phase extraction column, eluting with water-acetonitrile, 0.1% formic acid, to yield 0.114 g (73%) of the title compound.

¹H-NMR (DMSO) δ: 1.28 (3H, t), 1.40-1.55 (2H, m), 1.71-1.85 (2H, m), 2.20-2.60 (6H, m), 3.22 (2H, m), 4.28 (2H, q), 5.00-5.60 (2H, brs), 6.21 (1H, t), 6.92 (1H, d), 7.40-7.80 (8H, m), 8.50 (1H, d).

ESI-MS m/z: 519 (M + 1).

Example 424:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(ethoxycarbonylmethyl)-oxycarbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

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The procedure of Example 423 was followed, but replacing ethanol with ethyl glyoxylate to yield 0.041 g (26%) of the title compound.

¹H-NMR (DMSO) δ: 1.10-1.30 (3H, m), 1.35-1.55 (2H, m),
 5 1.60-1.85 (2H, m), 2.20-2.60 (6H, m), 3.32 (2H, m), 4.05-
 4.25 (2H, m), 4.87 (2H, s), 5.00-5.60 (2H, brs), 6.21 (1H,
 t), 6.92 (1H, d), 7.2-7.90 (8H, m), 8.50 (1H, d).
 ESI-MS m/z: 577 (M + 1).

Example 425:

10 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-

cyclohexyloxy carbonyl-[1]benzoxepino[2,3-b]pyridin-5-

ylidene) propyl]piperidine-4-ol

The procedure of Example 423 was followed, but replacing ethanol with cyclohexanol to yield 0.050 g (32%) of the title compound.

¹H-NMR (MeOD) δ: 1.30-2.20 (14H, m), 2.53-2.60 (2H, m),
 15 2.95-3.32 (6H, m), 5.00 (1H, m), 5.00-5.60 (2H, brs), 6.28
 (1H, t), 6.92 (1H, d), 7.40-7.55 (8H, m), 7.95 (2H, m),
 8.05 (1H, s), 8.50 (2H, m).
 20 ESI-MS m/z: 573 (M + 1).

Example 426:
 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-
 propoxy)carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene)

propyl]piperidine-4-ol

To a solution of the compound of Example 118 (109 mg, 0.22 mmol) in dry DMP (5 mL) was added potassium carbonate (91 mg) followed by propyl iodide (24 μL, 0.66 mmol). The mixture was heated to 55°C for 14 hours. The mixture was diluted with ethyl acetate (200 mL), washed twice with water (200 mL) and then with brine (100 mL), and dried with sodium sulfate. The organic solvent was removed

under reduced pressure and the residue subjected to silica gel chromatography using a dichloromethane : methanol gradient (0 to 5% MeOH over 1 hour) to give the title compound (103 mg).

¹H-NMR (CDCl₃) δ: 1.06 (3H, t), 1.50-2.10 (4H, m), 2.14-
 5 2.25 (2H, m), 2.31-2.75 (10H, m), 4.28 (2H, t), 6.15 (1H,
 t), 6.83 (1H, d), 7.24-7.38 (3H, m), 7.42 (2H, d), 7.59
 (1H, dd), 7.78 (1H, dd), 8.00 (1H, d), 8.50 (1H, dd).
 MS m/z: 533

Example 427:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1-
 butoxy)carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene)

propyl]piperidine-4-ol

The procedure of Example 423 was followed, but replacing ethanol with n-butanol to yield 0.065 g (45%) of the title compound.

¹H-NMR (MeOD) δ: 0.85-0.91 (3H, m), 1.25-1.45 (2H,
 m), 1.55-1.70 (2H, m), 1.70-1.85 (2H, m), 2.10-2.28 (2H,
 m), 2.53-2.60 (2H, m), 3.15-3.38 (6H, m), 4.12-4.21 (2H,
 m), 5.00-5.60 (2H, brs), 6.10 (1H, t), 6.76 (1H, d), 7.22-
 20 7.40 (3H, m), 7.71 (1H, m), 7.95 (1H, m), 8.05 (1H, s),
 8.30 (1H, s), 8.41 (1H, m).
 ESI-MS m/z: 547 (M + 1).

Example 428:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-
 propoxy)carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene)

propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with 30 2-bromopropane.

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¹H-NMR (CDCl₃) δ: 1.30-2.10 (8H, m), 2.14-2.25 (2H, m), 2.31-2.75 (10H, m), 5.15-5.60 (2H, m), 6.15 (1H, t), 6.83 (1H, d), 7.24-7.38 (3H, m), 7.44 (2H, d), 7.59 (1H, dd), 7.80 (1H, dd), 8.02 (1H, d), 8.50 (1H, dd).

5 MS m/z: 533

Example 429:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-cyclopentyl-oxy carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

10 The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with cyclopentyl borinate.

¹H-NMR (MeOD) δ: 1.23-1.33 (1H, m), 1.50-2.04 (10H, m), 2.27-2.41 (2H, m), 2.70-2.90 (2H, m), 3.30-3.62 (5H, m), 5.21-5.85 (3H, m), 6.15 (1H, t), 6.85 (1H, d), 7.38 (2H, d), 7.42 (2H, d), 7.60-7.82 (2H, m), 8.04 (1H, d), 8.61 (1H, dd).
MS m/z: 559

Example 430:

20 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-morpholinoethyl-1-yl)-oxy carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with 25 2-morpholinoethyl chloride.

¹H-NMR (CDCl₃) δ: 1.62-1.70 (2H, m), 1.90-2.13 (2H, m),

2.30-2.80 (14H, m), 3.62-3.75 (4H, m), 4.41 (2H, t), 5.11-5.62 (2H, brs), 6.19 (1H, t), 6.83 (1H, d), 7.23-7.38 (3H, m), 7.42 (2H, d), 7.59 (1H, dd), 7.78 (1H, dd), 8.00 (1H, d), 8.50 (1H, dd).

30 MS m/z: 604

Example 431:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2,2-diethylaminoethyl-1-yl)-oxy carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The titled compound was prepared by following the procedure of Example 426, but replacing propyl iodide with 2-(N,N-diethylamino)ethyl chloride.

¹H-NMR (CDCl₃) δ: 1.06 (6H, t), 1.62-1.71 (2H, m), 1.93-2.10 (2H, m), 2.30-2.75 (12H, m), 2.85 (2H, t), 4.38 (2H, t), 5.20-5.58 (2H, brs), 6.15 (1H, t), 6.83 (1H, d), 7.24-7.38 (3H, m), 7.42 (2H, d), 7.59 (1H, dd), 7.78 (1H, dd), 8.00 (1H, d), 8.50 (1H, dd).

MS m/z: 590

Example 432:

15 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(1,2,2-dimethylpropionyl-oxy methyl)-oxy carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

The procedure of Example 426 was followed, but 20 replacing with chloromethyl pivalate to yield 0.36 g (77%) of the title compound.

¹H-NMR (CDCl₃) δ: 1.18 (9H, s), 1.58-1.72 (2H, m), 1.85-2.85 (10H, m), 5.00-5.60 (2H, brs), 5.94 (2H, s), 6.17 (1H, t), 6.82 (1H, d), 7.22-7.42 (5H, m), 7.56 (1H, dd), 7.80 (1H, dd), 7.99 (1H, d), 8.05 (1H, d), 8.46 (1H, dd).
ESI-MS m/z: 605 (M + 1).

Example 433:

4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-(2-hydroxyethyl-1-yl)-oxy carbonyl-[1]benzoxepino[2,3-b]pyridin-5-ylidene) propyl]piperidine-4-ol

30 MS m/z: 604

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The procedure of Example 423 was followed, but replacing ethanol with ethylene glycol to yield 0.076 g (42%) of the title compound.

¹H-NMR (MeOD) δ: 1.80-2.00 (4H, m), 2.25-2.35 (2H, m),
5 2.55-2.65 (2H, m), 3.15-3.45 (5H, m), 3.75 (2H, dd), 4.24 (2H, dd), 5.00-5.60 (2H, brs), 6.10 (1H, t), 6.76 (1H, d), 7.18-7.42 (5H, m), 7.71 (2H, m), 7.99 (1H, m), 8.05 (1H, s), 8.30 (1H, s), 8.41 (1H, m).
ESI-MS m/z: 535 (M + 1).

10 Examples 4-7, 9-11, 13-16, 20, 80-82, 84, 87-88, 92-110, 112-113, 116, 119, 121, 124-127, 129, 136-137, 189, 193-195, 201, 202, 204, 206-210, 213-214, 216-217, 233, 236, 238-241, 243-247, 250-251, 257-259, 264-268, 270-272, 276-278, 282-287, 298-304, 305, 307-309, 313, 315, 327 and
15 337-344 shown in Figures 6 and 11 can be prepared by the schemes set forth in Figures 1 - 5, 7, 8A-8C, 9A-9E, 10A-10d, 12 and 13 and by the procedures described above.

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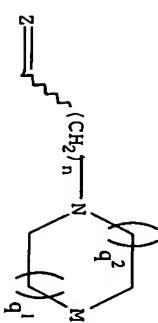
Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

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CLAIMS

What is claimed:

1. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



-C(=O)O-(aliphatic group), -C(=O)O-(substituted aliphatic group), -COOH, -CN, -CO-NR³R⁴, -NR³R⁴ or R¹ is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

5 R² is -OH, an acyl group, a substituted acyl group, -NRR⁶, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group,

-O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

10 R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aromatic group, a benzyl group, a substituted substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

15 R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

20 Z is represented by:

10 wherein:

n is an integer from one to about four;

M is >NR², >CR¹R², -O-CR¹R²-O- or -CH₂-CR¹R²-O-;

The ring containing M is substituted or unsubstituted;

15 q¹ is an integer, such as an integer from zero to about three;

q² is an integer from zero to about one;

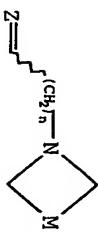
R¹ is -H, -OH, -N₃, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group),

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wherein:

X_1 is a bond, -O-, -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂HI-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO- or -CO-NR_c-;



R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

10 Ring A and Ring B are independently substituted or unsubstituted.

2. The method of Claim 1 wherein

15 R¹ is -H, -OH, -N₃, -CN, a halogen, a substituted aliphatic group, an aminoalkyl group -O-(aliphatic group), -O-(substituted aliphatic group), -NR³R⁴ or R¹

is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

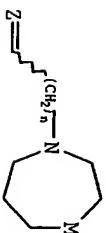
20 R² is -NR⁵R⁶, a substituted acyl group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, -O-(substituted or unsubstituted aromatic group); or

R¹ and R² taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

3. The method of Claim 1 wherein q¹ and q² are zero, and the compound is represented by the structural formula:

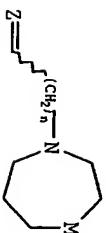
5 4. The method of Claim 3 wherein M is >CR¹R².

5. The method of Claim 1 wherein q¹ is one and q² is zero, and the compound is represented by the structural formula:



10 6. The method of Claim 5 wherein M is >CR¹R².

7. The method of Claim 1 wherein q¹ is one and q² is two, and the compound is represented by the structural formula:

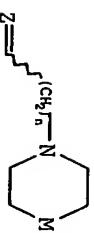


15 8. The method of Claim 7 wherein M is >NR².

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9. The method of Claim 1 wherein q¹ is one and q² is two, and the compound is represented by the structural formula:



-O-CH₂⁻, -CH₂-O-, -NR_c-CH₂⁻, -CH₂-NR_c⁻, -SO-CH₂⁻, -CH₂-S0-, -S(O)₂-CH₂⁻, -CH₂-S(O)₂⁻, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c-;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

5 10. The method of Claim 9 wherein M is -O-CR¹R²-O- or



11. The method of Claim 9 wherein

M is >NR² or >CR¹R²; and

R¹ is a substituted aliphatic group or an aminoalkyl group.

10

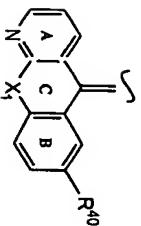
12. The method of Claim 9 wherein

M is >NR² or >CR¹R²; and

R² is -O-(substituted or unsubstituted aromatic group).

15

13. The method of Claim 1 wherein Z is represented by the structural formula:



wherein R⁴⁰ is -OH, -COOH, -NO₂, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, -NR²¹R²⁵, -CONR²¹R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group),

-O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHCO(O)O-R²⁰,

wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-,

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R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)-, -NR²⁴S(O)₂- or -C(O)O-;

R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

t is an integer from zero to about 3.

15. The method of Claim 14 wherein R⁴⁰ is represented by

-S(O)₂-NR²¹R²².

16. The method of Claim 15 wherein u is zero and t one to about three.

17. The method of Claim 15 wherein u is one and t is zero.

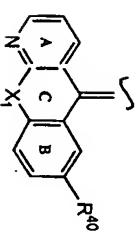
18. The method of Claim 15 wherein u and t are both zero.

19. The method of Claim 14 wherein R⁴⁰ is a aliphatic group that is substituted with -NR²⁴R²⁵ or -CONR²⁴R²⁵.

20. The method of Claim 14 wherein R⁴⁰ is -O-(aliphatic group) or -O-(substituted aliphatic group).

21. The method of Claim 14 wherein R⁴⁰ is -COOH.

22. The method of Claim 13 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X₁ in ring C, and Z is represented by the structural formula:



wherein R⁴⁰ is -C(=NR⁶⁰)NR²¹R²², -O-C(O)-NR²⁴R²⁶, -S(O)₂-NR²¹R²² or -N-C(O)-NR²¹R²²; wherein

R²¹ and R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

15. R²⁶ is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), -S(O)₂-(substituted or unsubstituted aliphatic group), -S(O)₂-(substituted or unsubstituted aromatic group); or

R²⁶ and R²¹, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

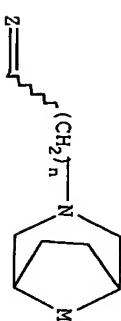
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23. The method of Claim 1 wherein X_1 is $-\text{CH}_2\text{O}-$.

24. A method of treating a disease associated with

aberrant leukocyte recruitment and/or activation,
comprising administering to a subject in need thereof
an effective amount of a compound represented by the
following structural formula:



and physiologically acceptable salts thereof,

wherein:

n is an integer from one to about four;

M is $>\text{NR}^1$, $>\text{CR}'\text{R}^2$, $-\text{O}-\text{CR}'\text{R}^2-\text{O}-$ or $-\text{CH}_2\text{CR}'\text{R}^2\text{O}-$;

The ring containing M is substituted or
unsubstituted;

R^1 is $-\text{H}$, $-\text{OH}$, $-\text{N}_3$, a halogen, an aliphatic group,

a substituted aliphatic group, an aminoalkyl group,
 $-\text{O}-$ (aliphatic group), $-\text{O}-$ (substituted aliphatic

group), $-\text{SH}$, $-\text{S}-$ (aliphatic group), $-\text{S}-$ (substituted
aliphatic group), $-\text{OC(O)}-$ (aliphatic group),

$-\text{O}-\text{C(O)}$ -(substituted aliphatic group),
 $-\text{C(O)O}-$ (aliphatic group), $-\text{C(O)O}-$ (substituted
aliphatic group), $-\text{COOH}$, $-\text{CN}$, $-\text{CO-NRR}'$, $-\text{NRR}'\text{R}^4$ or R^1

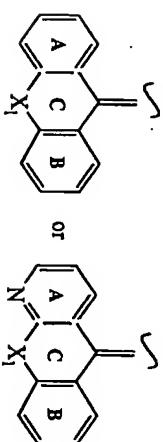
is a covalent bond between the ring atom at M and an
adjacent carbon atom in the ring which contains M ;

10

R^1 and R^2 , R^3 and R^4 , or R^5 and R^6 taken together

with the atom to which they are bonded, form a
substituted or unsubstituted non-aromatic carbocyclic
or heterocyclic ring;

15 Z is represented by:



wherein:

X_1 is $-\text{S}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{S}-$, $-\text{SCH}_2-$,
 $-\text{O}-\text{CH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{NR}_e\text{CH}_2-$, $-\text{CH}_2\text{NR}_e-$, $-\text{SO}-\text{CH}_2-$,

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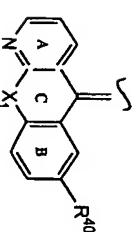
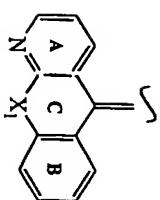
-CH₂-SO⁻, -S(O)₂-CH₂⁻, -CH₂-S(O)₂⁻, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c⁻;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

5

25. The method of Claim 24 wherein z is represented by the structural formula:



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂O-, -NR_c-CH₂-, -CH₂-NR_c⁻, -SO-CH₂-, -CONR²⁴R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group),

10 -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰,

15 -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁰,

R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

20 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)-, -NR²⁴S(O)₂⁻ or -C(O)O-;

25 R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

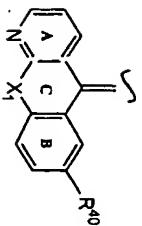
26. The method of Claim 25 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X₁ in ring C, and z is represented by the structural formula:

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u is zero or one; and
t is an integer from zero to about 3.

27. The method of Claim 25 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_1 , in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{50})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{22}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

10 R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

15 R^{21} and R^{22} , taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{25} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, or a covalent bond between the nitrogen atom and an adjacent carbon atom;

20 R^3 and R^4 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

25

28. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof,

wherein:

n is an integer from one to about four;

10 R^{50} and R^{51} are each, independently, -H, R^{31} and R^{32} are each independently -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, $-NR^3R'$, an aromatic group, a substituted aromatic group; a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, or a covalent bond between the nitrogen atom and an adjacent carbon atom;

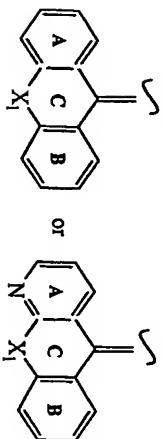
15 R^3 and R^4 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;

20

R^{26} and R^{21} , taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

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z is represented by:



wherein:

5 X_1 is $-S-$, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$,
 $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$,
 $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, $-CH=CH-$, $-NR_c-CO-$, a
 bond, $-O-$, or $-CO-NR_c-$;

R_c is $-H$, an aliphatic group, a substituted
 aliphatic group, an aromatic group, a substituted
 aromatic group, a benzyl group or a substituted
 benzyl group; and

Ring A and Ring B are independently substituted or
 unsubstituted.

29. The method of Claim 28 wherein

R³⁰ is a substituted aliphatic group; and

15 R³¹ is $-H$, an aliphatic group or a substituted
 aliphatic group.

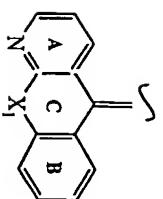
30. The method of Claim 29 wherein R³⁰ is a substituted
 aliphatic group bearing an aromatic substituent.

20 31. The method of Claim 29 wherein R³⁰ is a an aliphatic
 group which is substituted with a 4-chlorophenyl

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z is represented by:

32. The method of Claim 28 wherein z is represented by
 the structural formula:



wherein:

5 X_1 is $-S-$, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-S-$, $-S-CH_2-$,
 $-O-CH_2-$, $-CH_2-O-$, $-NR_c-CH_2-$, $-CH_2-NR_c-$, $-SO-CH_2-$,
 $-CH_2-SO-$, $-S(O)_2-CH_2-$, $-CH_2-S(O)_2-$, $-CH=CH-$, $-NR_c-CO-$, a
 bond, $-O-$, or $-CO-NR_c-$;

R_c is $-H$, an aliphatic group, a substituted
 aliphatic group, an aromatic group, a substituted
 aromatic group, a benzyl group or a substituted
 benzyl group; and

Ring A and Ring B are independently substituted or
 unsubstituted.

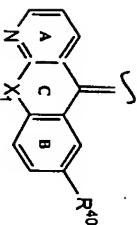
-240-

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33. The method of claim 32 wherein step B is substantially

...
para to the carbon atom of ring B that is bonded to X in ring C, and Z is represented by the structural formula:

5



wherein R⁴⁰ is -OH, -COOH, -NO₂, halogen, aliphatic

group, a substituted aromatic group, $-NR^2R^5$, $-CONR^2R^2$, Q-(aliphatic group), Q-(substituted aliphatic group), O-(aliphatic group),

group), $-\text{O}-$ (substituted aromatic group), an electron withdrawing group, $-(\text{O})_u-(\text{CH}_2)_t-\text{C}(\text{O})\text{OR}^{20}$, $-(\text{O})_u-(\text{CH}_2)_t-\text{OC}(\text{O})\text{R}^{20}$, $-(\text{O})_u-(\text{CH}_2)_t-\text{C}(\text{O})-\text{NR}^{21}\text{R}^{22}$ or $-(\text{O})_u-(\text{CH}_2)_t-\text{NHC}(\text{O})\text{OR}^{20}$;

" R_1 and R_2 are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

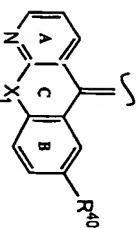
to which they are bonded, form a non-aromatic heterocyclic ring;

Q is $-NR^2C(O)-$, $-NR^2S(O)_2-$ or $-C(O)O-$;
 R^2 and R^3 are independently $-H$, $-OH$, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

t is an integer from zero to eight?

34. The method of Claim 32 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_1 in ring C, and Z is represented by the structural formula:



wherein R⁶⁰ is -C(=NR⁶⁰)NR²¹R²², -O-C(O)-NR²¹R²², -S(O)₂-NR²¹R²² or -N=C(O)-NPB²¹R²², wherein

R^{11} and R^{12} are independently $-H$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or
 R^{21} and R^{22} , taken together with the nitrogen atom to which they are bonded, form a substituted or

13

20 R²⁶ is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic ring; -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), -S(O)₂- (substituted or unsubstituted aliphatic group), -S(O)₂- (substituted or unsubstituted aromatic group); or

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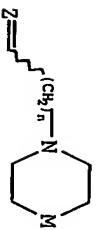
-243-

R^{26} and R^{21} , taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.



35. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation,

comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



or a physiologically acceptable salt thereof,

wherein:

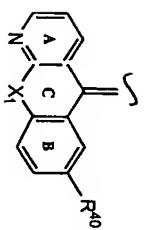
M is CR^1R^2 ;

R^1 is $-OH$;

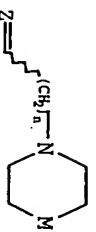
R^2 is 4-chlorophenyl;

n is two;

Z is represented by:



36. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



or a physiologically acceptable salt thereof,

wherein:

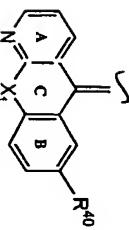
M is CR^1R^2 ;

R^1 is $-OH$;

R^2 is 4-chlorophenyl;

n is two;

Z is represented by:

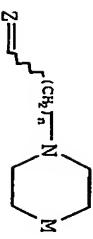


X_1 is $-CH_2-O-$; and
 R^{40} is

X_1 is $-CH_2-O-$; and
 R^{40} is $-COOH$.

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37. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



or a physiologically acceptable salt thereof, wherein:

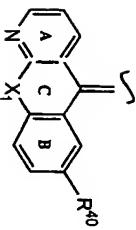
M is CR¹R²;

R¹ is -OH;

R² is 4-chlorophenyl;

n is two;

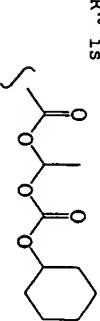
Z is represented by:



15

X₁ is -CH₂-O-; and

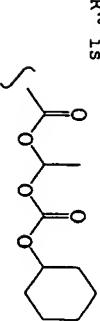
R⁴⁰ is



15

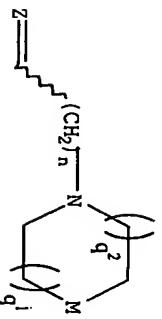
X₁ is -CH₂-O-; and

R⁴⁰ is



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38. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

n is an integer from one to about four;

M is >NR², >CR¹R², -O-CR¹R²-O- or -CH₂-CR¹R²-O-;

The ring containing M is substituted or unsubstituted;

R¹ is -H, -OH, -N₃, a halogen, an aliphatic group,

a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group),

-O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, -CO-NR³R⁴, -NR³R⁴ or R¹

is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R² is -OH, an acyl group, a substituted acyl group, -NR⁵R⁶, an aliphatic group, a substituted

aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, a substituted non-substituted aromatic group) or

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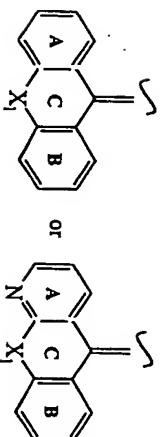
-247-

-O-(substituted or unsubstituted aliphatic group);

R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

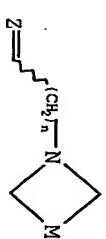
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39. The compound of Claim 38 wherein

R¹ is -H, -OH, -N₃, -CN, a halogen, a substituted aliphatic group, an aminoalkyl group -O-(aliphatic group), -O-(substituted aliphatic group), -NR³R⁴ or R¹ is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M; R² is -NRF⁶, a substituted acyl group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, -O-(substituted or unsubstituted aromatic group); or

R¹ and R² taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

40. The compound of Claim 38 wherein q¹ and q² are zero, and the compound is represented by the structural formula:



15

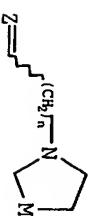
41. The compound of Claim 40 wherein M is >CR¹R², -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

20

42. The compound of Claim 38 wherein q¹ is one and q² is zero, and the compound is represented by the structural formula:



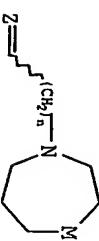
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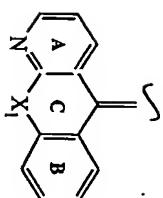
-249-

43. The compound of Claim 42 wherein M is >CR¹R².

44. The compound of Claim 38 wherein q¹ is one and q² is two, and the compound is represented by the structural formula:



5

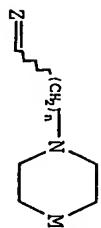


50.

The compound of Claim 38 wherein Z is represented by the structural formula:

45. The compound of Claim 44 wherein M is >NR².

46. The compound of Claim 38 wherein q¹ is one and q² is two, and the compound is represented by the structural formula:



10

wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a

bond, -O-, or -CO-NR_c-;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

15 Ring A and Ring B are independently substituted or unsubstituted.

47. The compound of Claim 46 wherein M is -O-CR¹R²-O- or -CH₂-CR¹R²-O-.

48. The compound of Claim 46 wherein

M is >NR² or >CR¹R²; and

15 R¹ is a substituted aliphatic group or an aminoalkyl group.

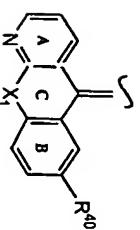
49. The compound of Claim 46 wherein

M is >NR² or >CR¹R²; and

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51. The compound of Claim 48 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X₁ in ring C, and Z is represented by the structural formula:



u is zero or one; and
t is an integer from zero to about 3.

52. The compound of Claim 51 wherein R⁴⁰ is represented by
 $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$.

53. The compound of Claim 52 wherein u is zero and t is about three.

54. The compound of Claim 52 wherein u is one and t is zero.

wherein R⁴⁰ is -OH, -COOH, -NO₂, halogen, aliphatic group, substituted aliphatic group, an aromatic

group, a substituted aromatic group, -NR²⁴R²⁵, -CONR²⁴R²⁵, O-(aliphatic group), Q-(substituted

10

aliphatic group), -O-(aliphatic group),

-O-(substituted aliphatic group), -O-(aromatic

group), -O-(substituted aromatic group), an electron

withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰,

-(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²⁴R²⁵ or

-(O)_u-(CH₂)_t-NHC(O)O-R²⁰,

15

R²⁰, R²¹ or R²² are independently -H, an aliphatic

group, a substituted aliphatic group, an aromatic

group, a substituted aromatic group or a non-aromatic

heterocyclic group; or

R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

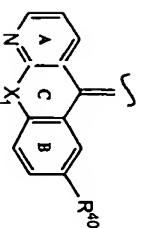
Q is -NR²⁴C(O)-, -NR²⁴S(O)₂- or -C(O)O-;

R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

25

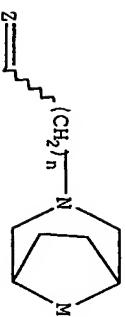
-252-

59. The compound of Claim 50 wherein ring B is substituted para to the carbon atom of ring C that is bonded to X₁ in ring C, and Z is represented by the structural formula:



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60. The compound of Claim 38 wherein X₁ is -CH₂-O-, M is >NR², >CR¹R², -O-CRR²-O- or -CH₂-CR¹R²-O-; The ring containing M is substituted or unsubstituted;



5 or physiologically acceptable salt thereof, wherein:

n is an integer from one to about four;
M is >NR², >CR¹R², -O-CRR²-O- or -CH₂-CR¹R²-O-;

The ring containing M is substituted or unsubstituted;

61. A compound represented by the following structural formula:

5
R¹ and R², taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

10 R¹⁶ is -H, an aliphatic group, a substituted heterocyclic group; or

R¹ and R², taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

15 R¹⁶ is -H, an aliphatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, -CO-NR³R⁴, -NRR⁴ or R¹ is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

20 R² is -OH, an acyl group, a substituted acyl group, -NRR⁶, an aliphatic group, a substituted aliphatic group, an aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group,

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-O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

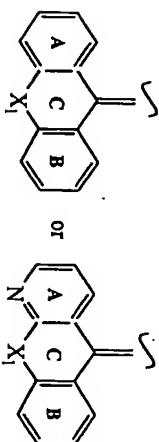
5 R³, R⁴, R⁵ and R⁶ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aromatic group, an aromatic group, a

substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

10 R¹ and R², R³ and R⁴, or R⁵ and R⁶ taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:

15



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-,

10 -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

wherein:

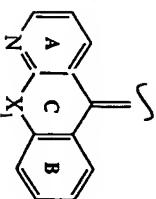
X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-,

-CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c;

20 R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

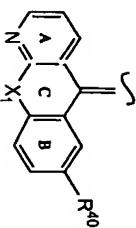
15 Ring A and Ring B are independently substituted or unsubstituted.

62. The compound of Claim 61 wherein Z is represented by the structural formula:



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63. The compound of Claim 62 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X₁ in ring C, and Z is represented by the structural formula:



wherein R⁴⁰ is -OH, -COOH, -NO, halogen, aliphatic group, substituted aliphatic group, an aromatic

group, a substituted aromatic group, -NR²⁴R²⁵, -CONR²⁴R²⁵, Q-(aliphatic group), Q-(substituted

aliphatic group), -O-(aliphatic group),

-O-(substituted aliphatic group), -O-(aromatic

group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁰,

-(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²¹R²² or

-(O)_u-(CH₂)_t-NHC(O)O-R²⁰;

R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic

group or a non-aromatic heterocyclic group; or

R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a substituted or

15 unsubstituted non-aromatic heterocyclic ring; wherein R²¹ is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, a substituted aromatic group, an aliphatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), -S(O)₂-(substituted or unsubstituted aliphatic group), -S(O)₂-(substituted or unsubstituted aromatic group); or

20 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)-, -NR²⁴S(O)₂- or -C(O)O-;

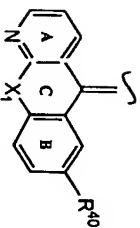
R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

25 u is zero or one; and

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t is an integer from zero to about 3.

64. The compound of Claim 62 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X₁ in ring C, and Z is represented by the structural formula:



5 wherein R⁴⁰ is -C(=NR⁶⁰)NR²¹R²², -O-C(O)-NR²¹R²⁶, -S(O)₂-NR²¹R²² or -N-C(O)-NR²¹R²², wherein

10 R²¹ and R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a substituted or

15 unsubstituted non-aromatic heterocyclic ring; wherein R²¹ is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, a substituted aromatic group, an aliphatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), -S(O)₂-(substituted or unsubstituted aliphatic group), -S(O)₂-(substituted or unsubstituted aromatic group); or

20 R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)-, -NR²⁴S(O)₂- or -C(O)O-;

R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

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R²⁶ and R²¹, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

5. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

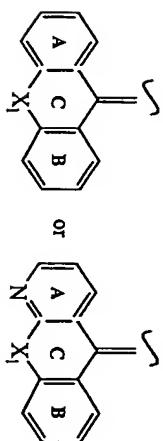
n is an integer from one to about four;

10 R⁵⁰ and R⁵¹ are each, independently, -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -NRR⁴, an aromatic group, a substituted aromatic group, a benzyl group, a

15 substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, or a covalent bond between the nitrogen atom and an adjacent carbon atom;

R³ and R⁴ are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group;

Z is represented by:



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c-,

15 R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

66. The compound of Claim 65 wherein

R⁵⁰ is a substituted aliphatic group; and

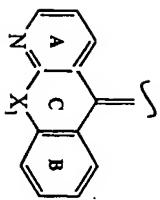
15 R⁵¹ is -H, an aliphatic group or a substituted aliphatic group.

67. The compound of Claim 66 wherein R⁵⁰ is a substituted aliphatic group bearing an aromatic substituent.

20 68. The method of Claim 66 wherein R⁵⁰ is a substituted aliphatic group that is substituted with a 4-chlorophenyl group.

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69. The compound of Claim 65 wherein z is represented by the structural formula:



wherein:

X₁ is -S-, -CH₂-, -CH₂-CH₂-, -CH₂-S-, -S-CH₂-, -O-CH₂-, -CH₂-O-, -NR_c-CH₂-, -CH₂-NR_c-, -SO-CH₂-, -CH₂-SO₂-, -S(O)₂-CH₂-, -CH₂-S(O)₂-, -CH=CH-, -NR_c-CO-, a bond, -O-, or -CO-NR_c;

R_c is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

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70. The compound of Claim 69 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X₁ in ring C, and z is represented by the structural formula:



5

wherein R⁴⁰ is -OH, -COOH, -NO₂, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, -NR²⁴R²⁵, -CONR²⁴R²⁵, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, -(O)_u-(CH₂)_t-C(O)OR²⁶, -(O)_u-(CH₂)_t-OC(O)R²⁰, -(O)_u-(CH₂)_t-C(O)-NR²⁴R²² or -(O)_u-(CH₂)_t-NHC(O)O-R²⁶,

R²⁰, R²¹ or R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is -NR²⁴C(O)-, -NR²⁴S(O)₂- or -C(O)O-;

R²⁴ and R²⁵ are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

25

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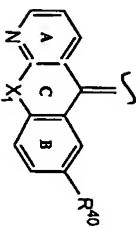
t is an integer from zero to about 3.

71. The compound of Claim 69 wherein ring B is

substituted para to the carbon atom of ring B that is

bonded to X₁ in ring C, and Z is represented by the

structural formula:



wherein R⁴⁰ is -C(=NR⁶⁰)NR²¹R²², -O-C(O)-NR²¹R²⁶,

-S(O)₂-NR²¹R²² or -N-C(O)-NR²¹R²⁶; wherein

R²¹ and R²² are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

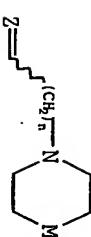
R²¹ and R²², taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

15 R²⁶ is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group,

-C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), -S(O)₂-(substituted or unsubstituted aliphatic group), -S(O)₂-(substituted or unsubstituted aromatic group); or

10 R²⁶ and R²¹, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

72. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

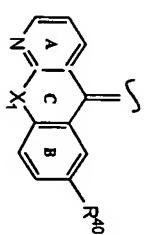
M is CR¹R²;

R¹ is -OH;

R² is 4-chlorophenyl;

n is two;

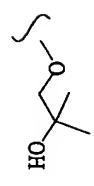
Z is represented by:



X₁ is -CH₂-O-; and

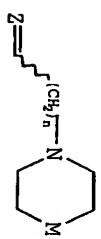
R⁴⁰ is

15 R⁴⁰ is



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73. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

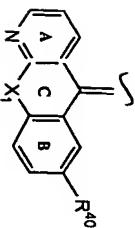
M is CR^1R^2 ;

R^1 is -OH;

R^2 is 4-chlorophenyl;

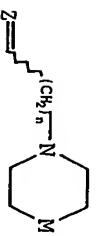
n is two;

Z is represented by:



X_1 is - $\text{CH}_2\text{-O}-$; and
 R^{40} is -COOH.

74. A compound represented by the following structural formula:



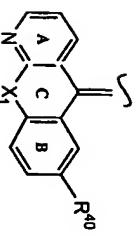
or physiologically acceptable salt thereof, wherein:

M is CR^1R^2 ;

R^1 is -OH;

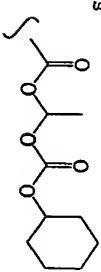
-265-

R² is 4-chlorophenyl;
n is two;
Z is represented by:

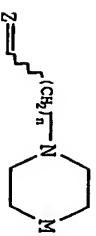


5

X₁ is - $\text{CH}_2\text{-O}-$; and
R⁴⁰ is



75. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

M is CR^1R^2 ;

R^1 is -OH;

R^2 is 4-chlorophenyl;

n is two;

Z is represented by:

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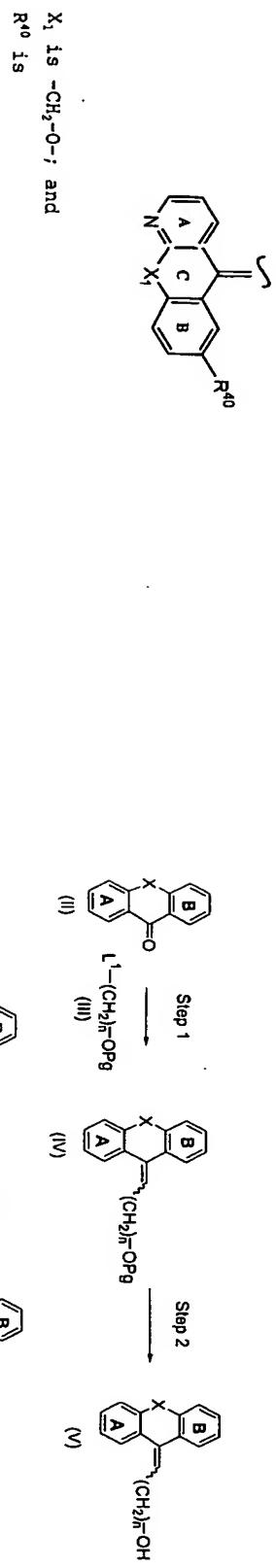


Figure 1

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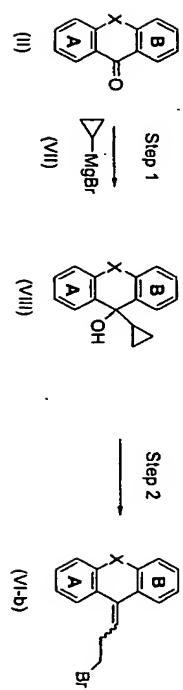


Figure 2

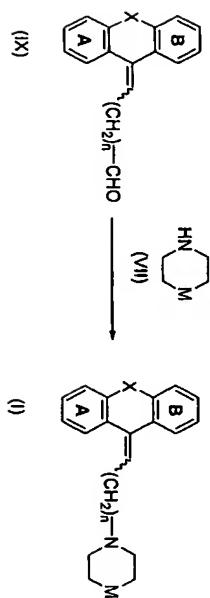


Figure 3

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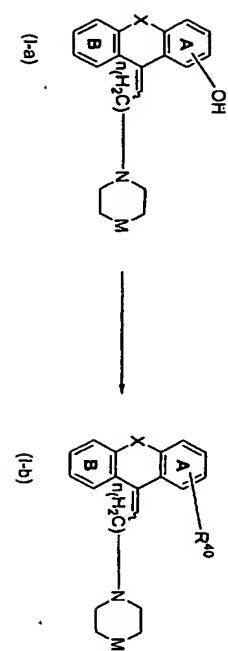


Figure 4

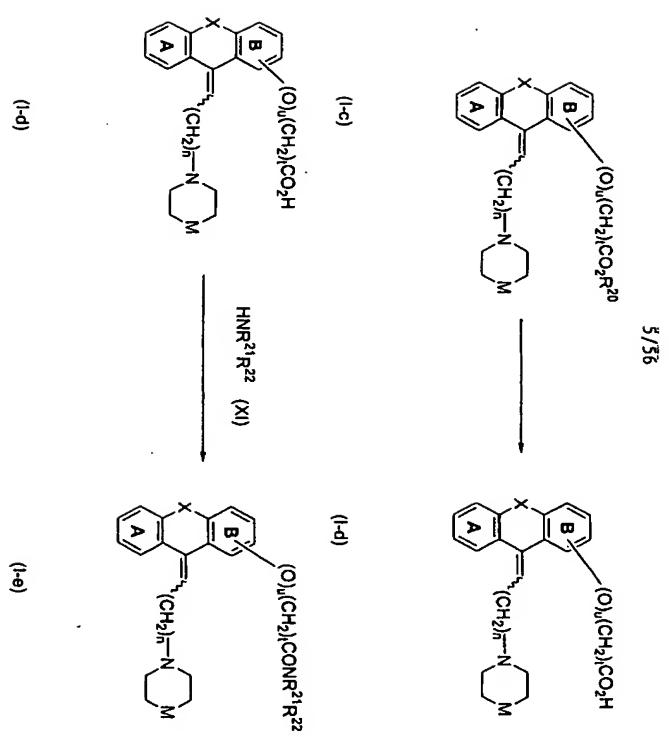


Figure 5

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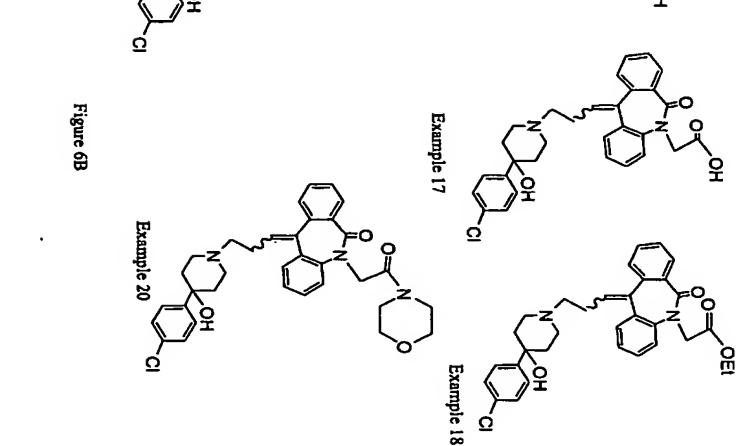
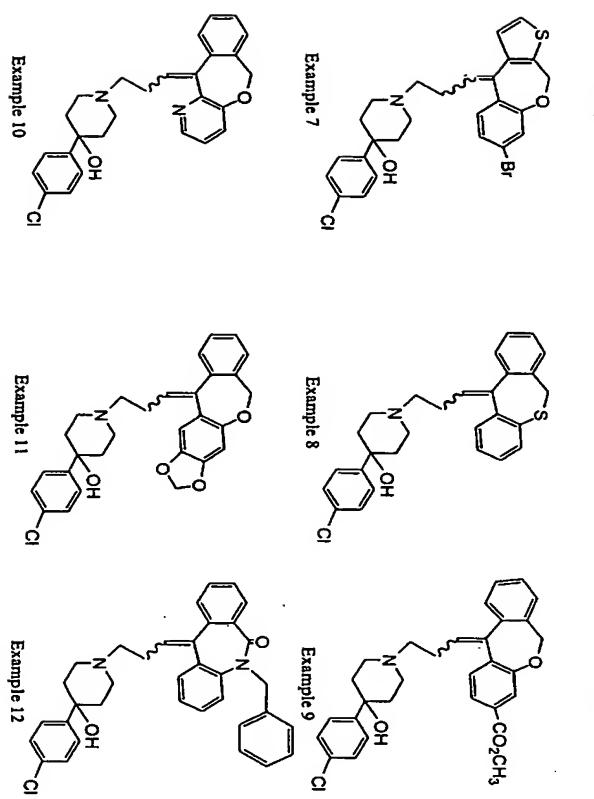
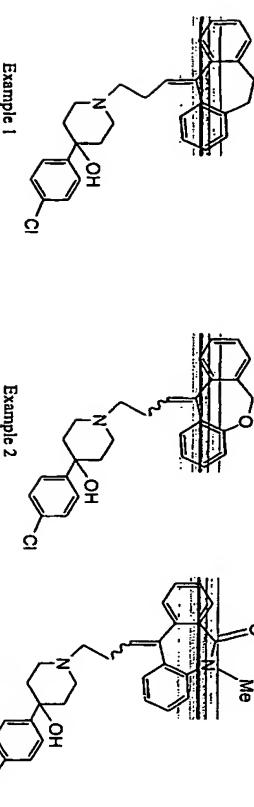


Figure 6A

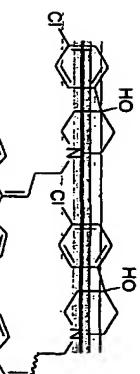
Figure 6B

WO 01/09138

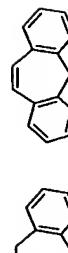
PCT/US00/20732

WO 01/09138

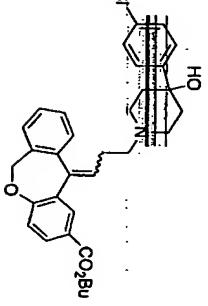
PCT/US00/20732



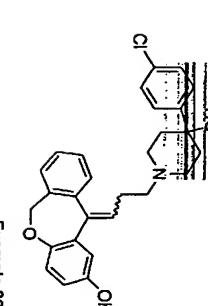
8/56



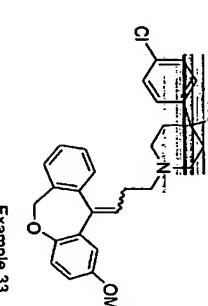
8/56



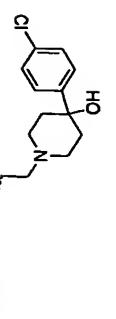
8/56



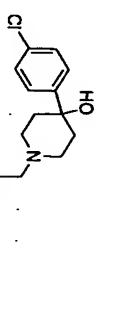
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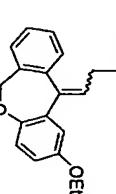
Example 24



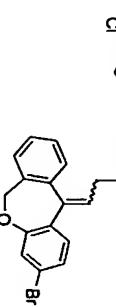
Example 25



Example 26



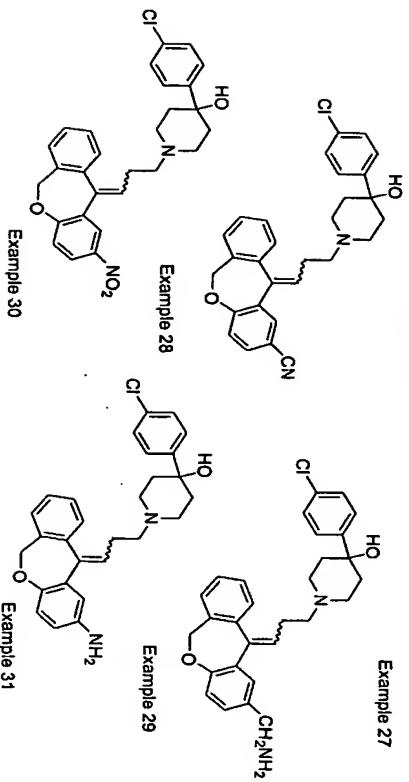
Example 27



Example 28



Example 29



Example 30

Example 31

Figure 6C

Figure 6D

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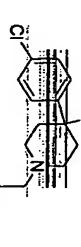
10/56



Example 39

PCT/US00/20732

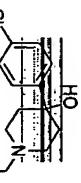
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Example 40

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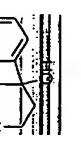
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Example 44

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Example 45

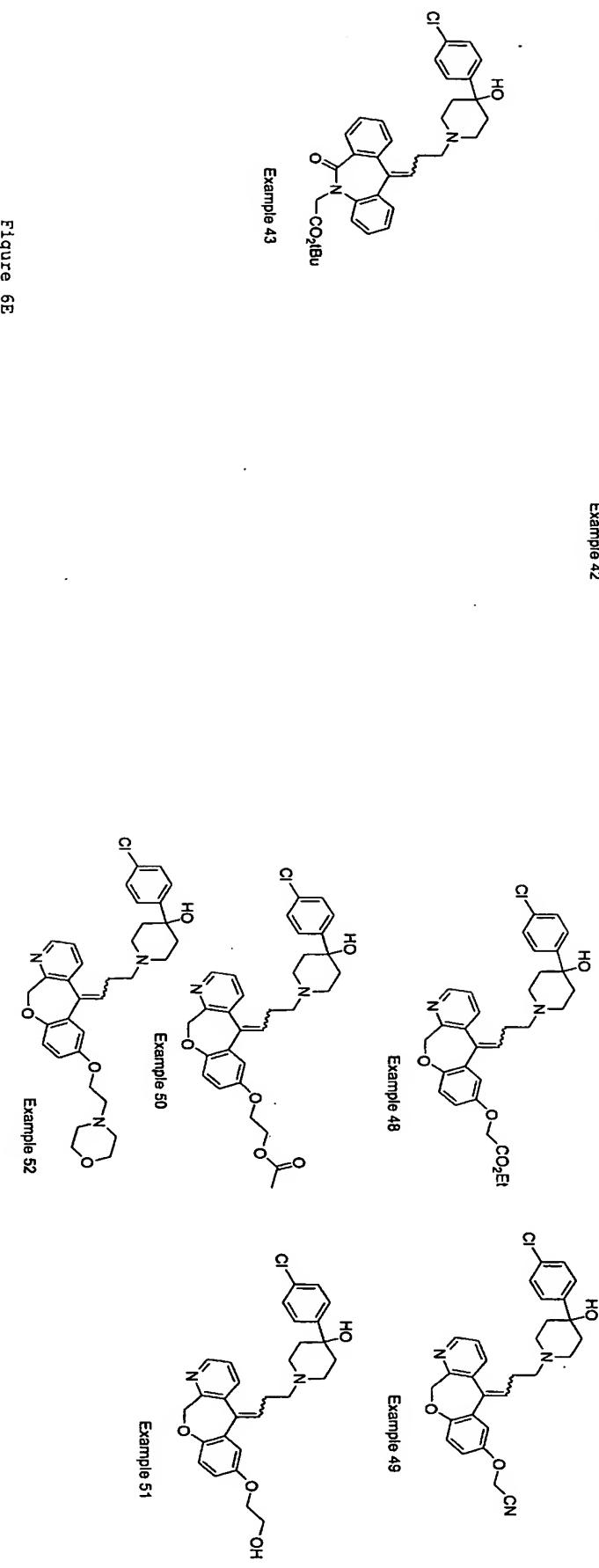


Figure 6E

Figure 6F

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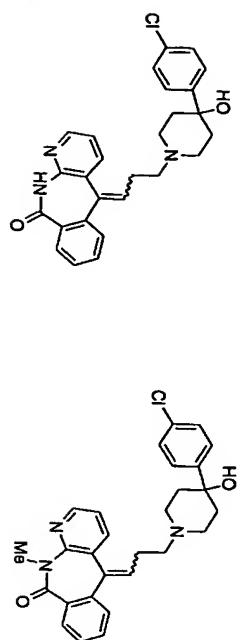
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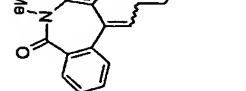


Example 53

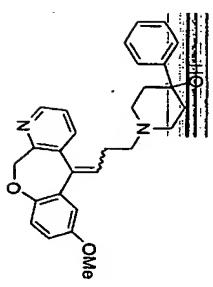
Example 54



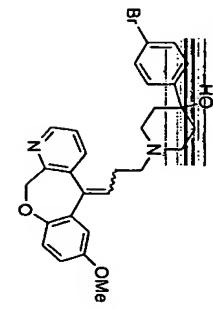
Example 55



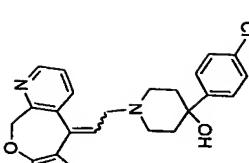
Example 56



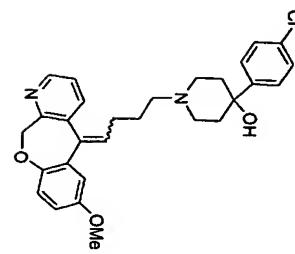
Example 59



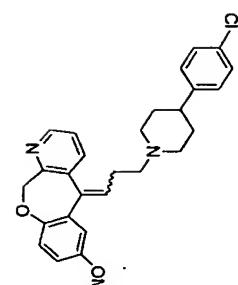
Example 60



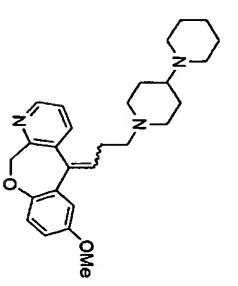
Example 57



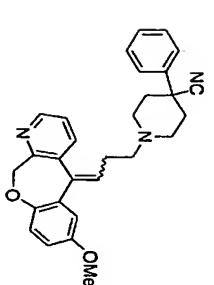
Example 58



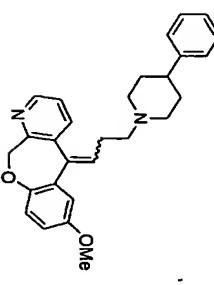
Example 63



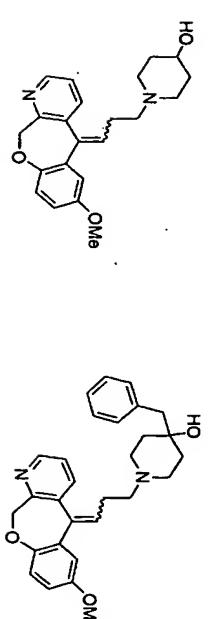
Example 65



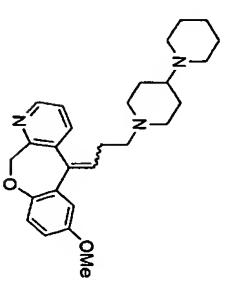
Example 61



Example 64



Example 62



Example 66

Figure 6G

Figure 6H

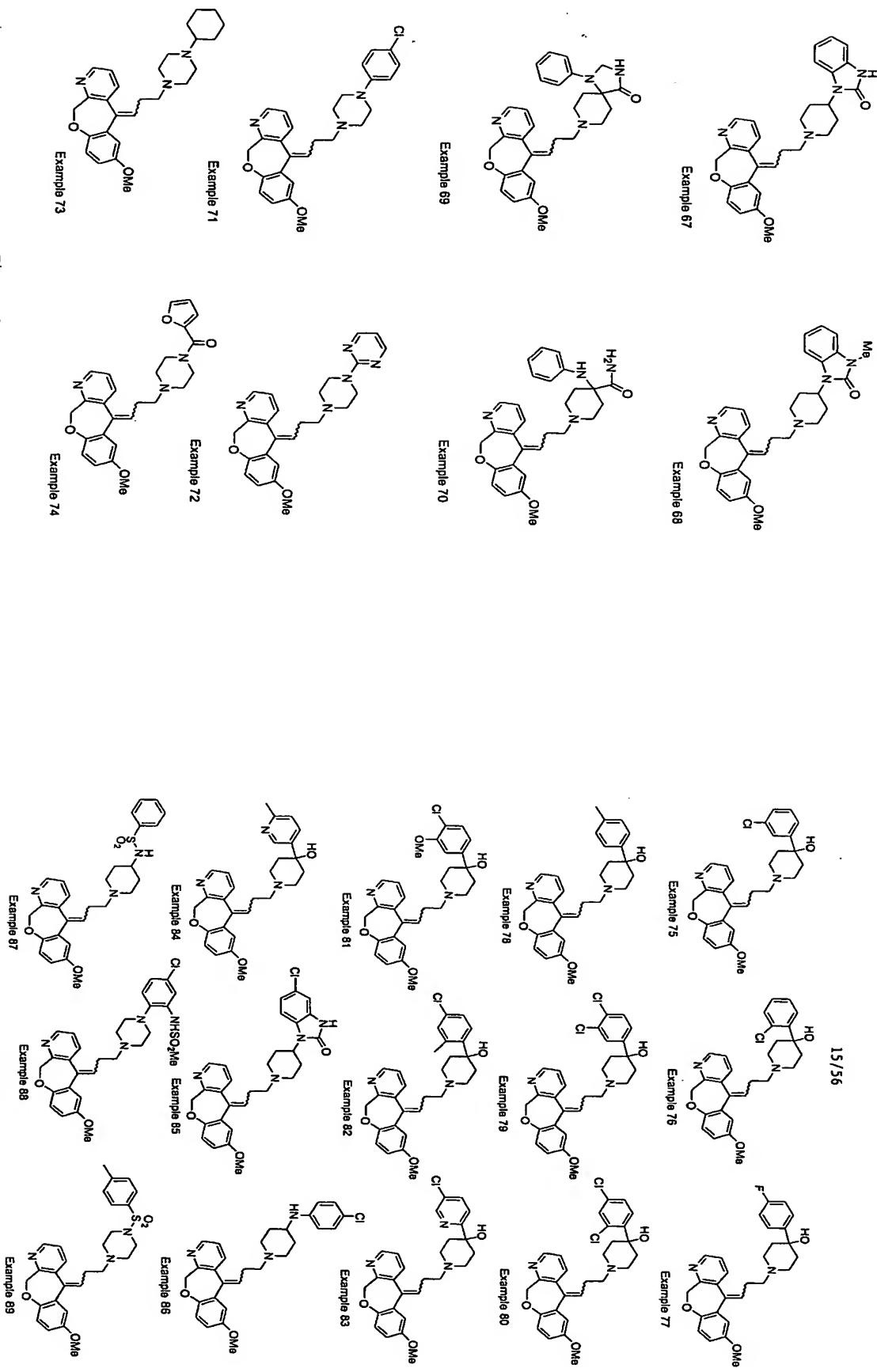


Figure 6I

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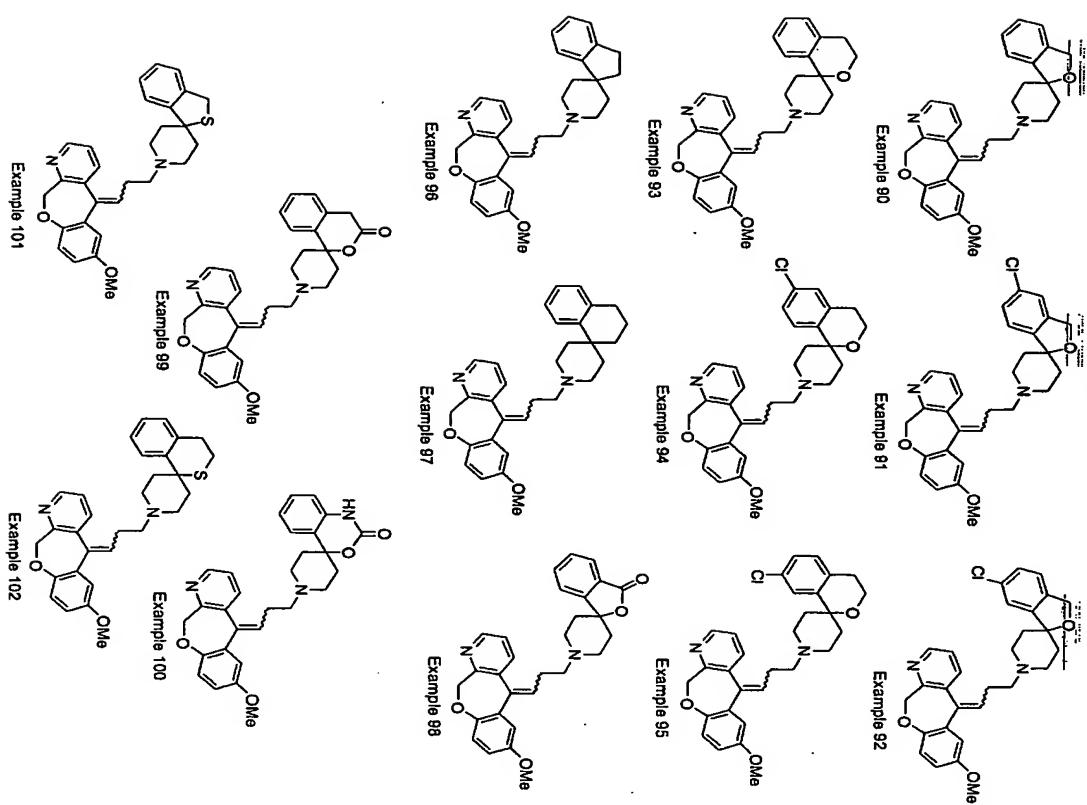
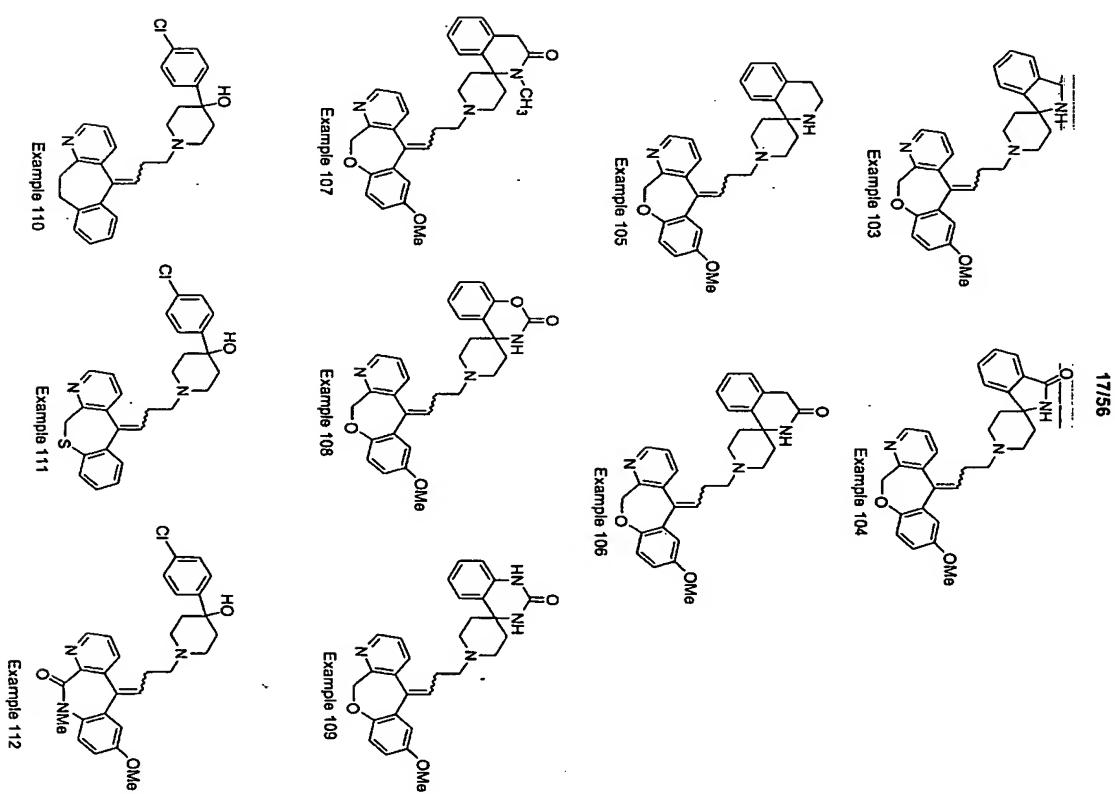


Figure 6K

Figure 6L



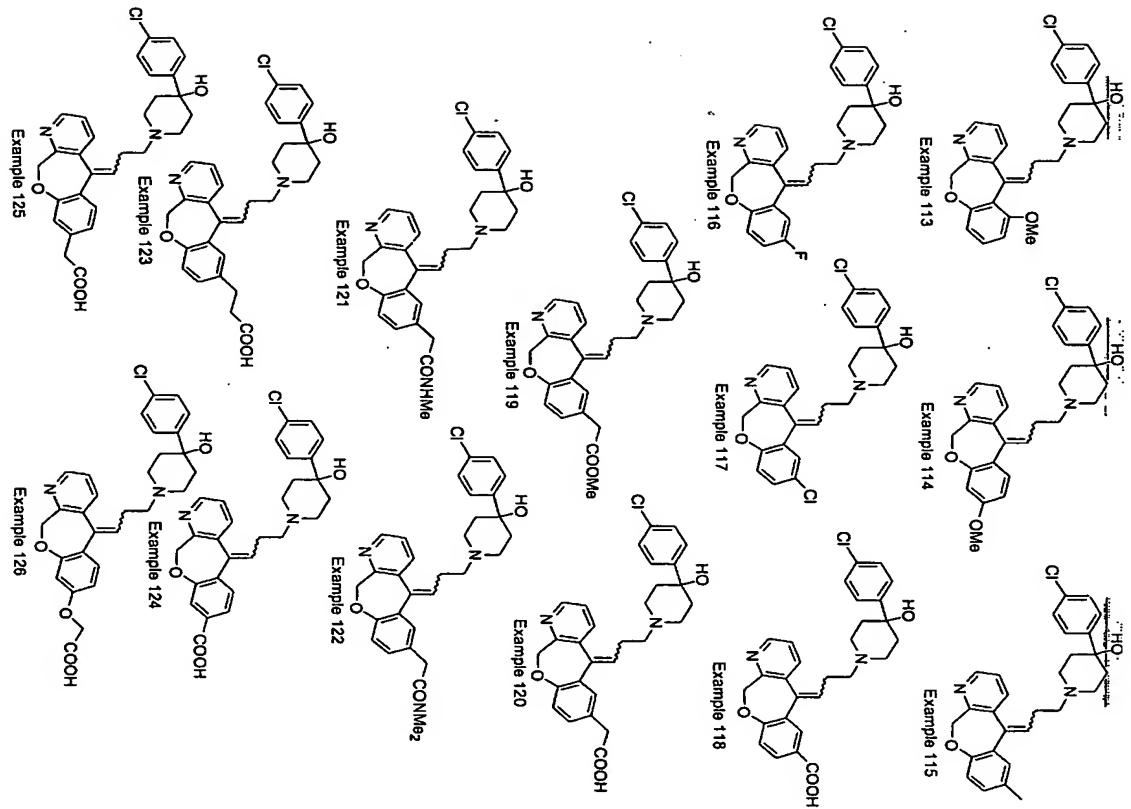


Figure 6M

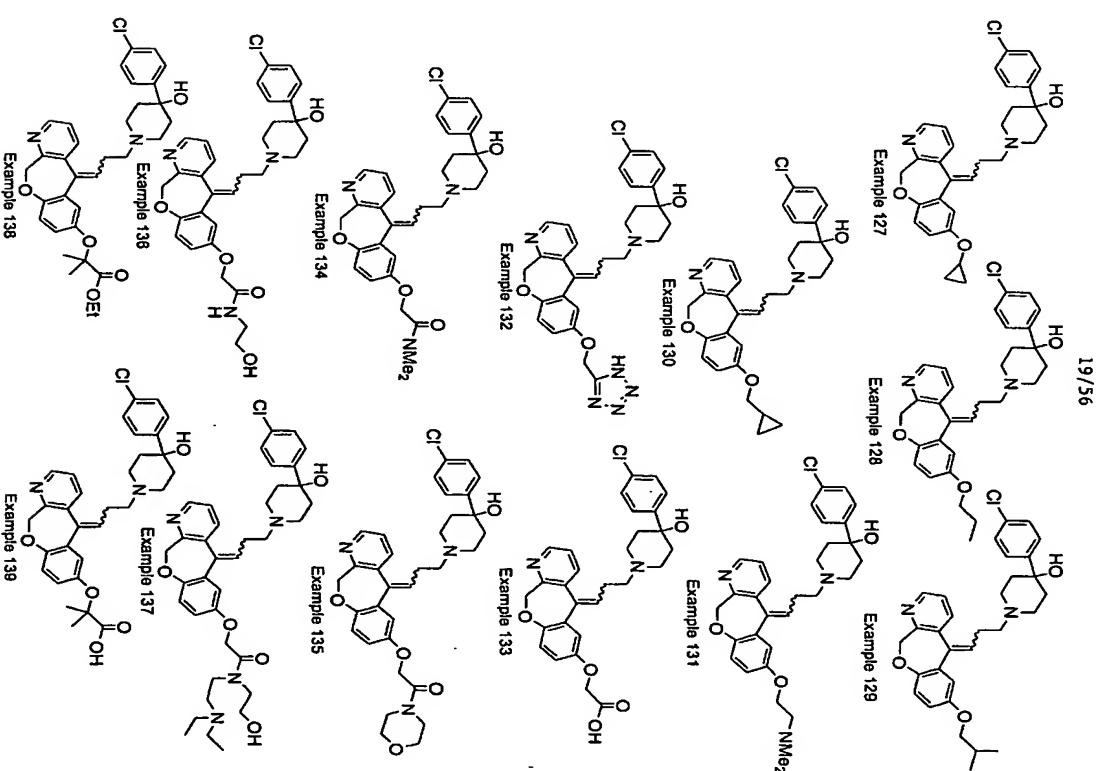


Figure 6N

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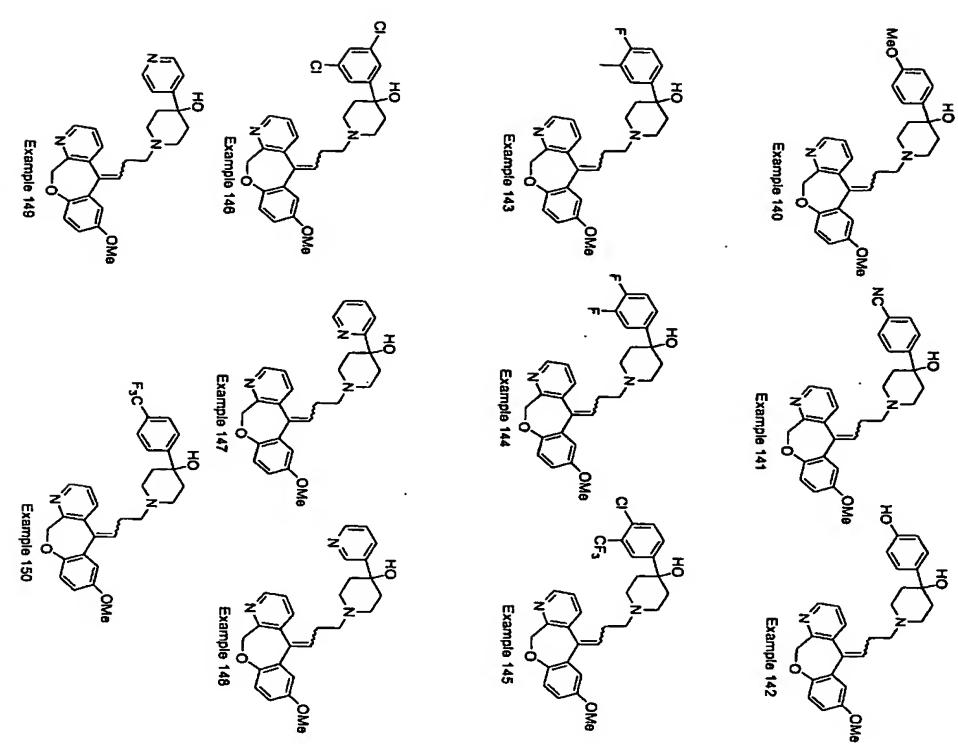
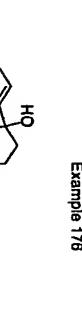
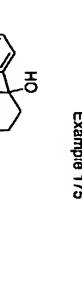
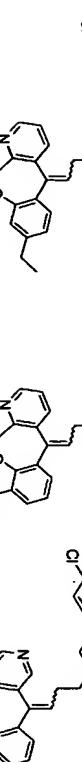
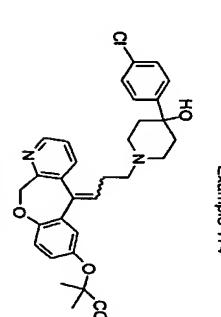
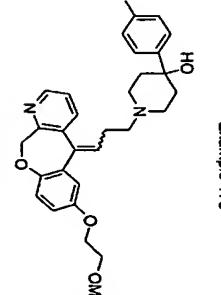
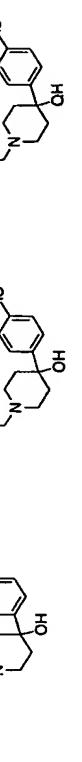
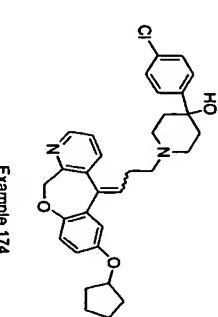
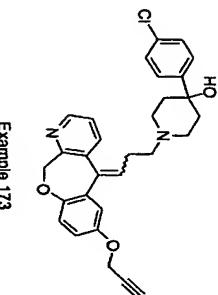
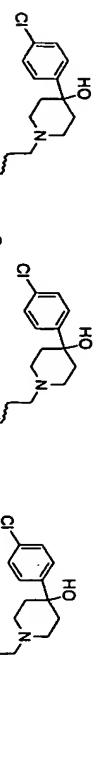


Figure 60

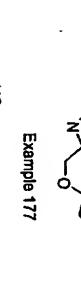
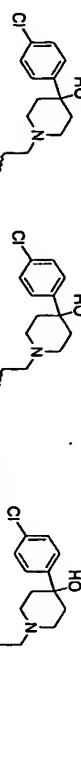
Figure 6P

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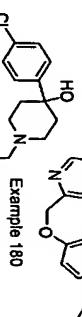
23/56



Example 165
Example 166
Example 167



Example 168
Example 169
Example 170



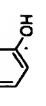
Example 173
Example 174
Example 175

Figure 6Q

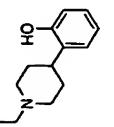
Figure 6R

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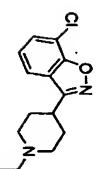
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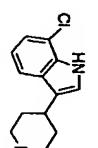
Example 183



Example 184



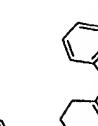
Example 185



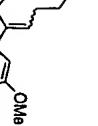
Example 186



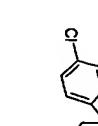
Example 187



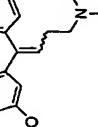
Example 188



Example 189



Example 190



Example 191



Example 192



Example 193

Example 194

Example 195

Example 196

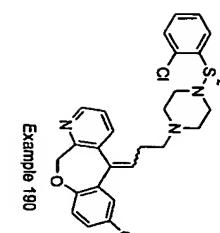
Example 197

Example 198

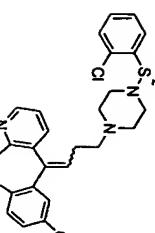
Example 199

Example 200

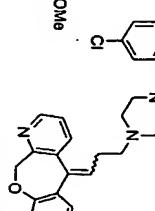
Figure 6S



Example 187



Example 188



Example 189

Example 190

Example 191

Example 192

Example 193

Example 194

Example 195

Example 196

Example 197

Example 198

Example 199

Example 200

Example 190

Example 191

Example 192

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Example 191

Example 192

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Example 197

Example 198

Example 199

Example 200

Example 190

Example 191

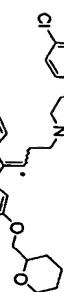
Example 192

Example 193

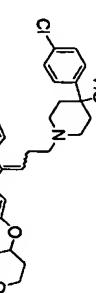
27/56



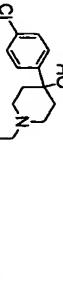
26/56



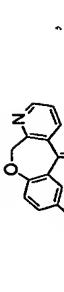
Example 201



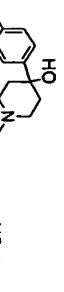
Example 202



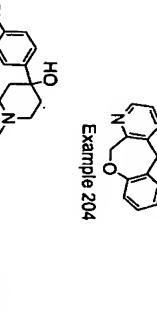
Example 203



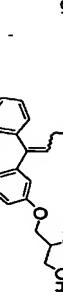
Example 204



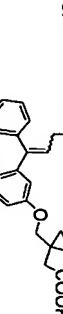
Example 205



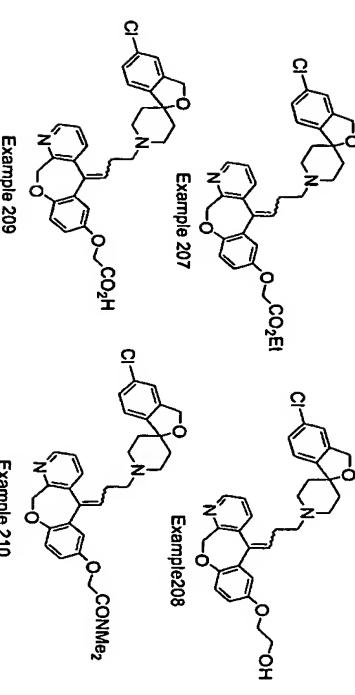
Example 206



Example 207



Example 208



Example 209

Example 210

Example 211

Example 212

Example 213

Example 214

Example 215

Example 216

Example 217

Example 218

Example 219

Example 220

Figure 6U

Figure 6V

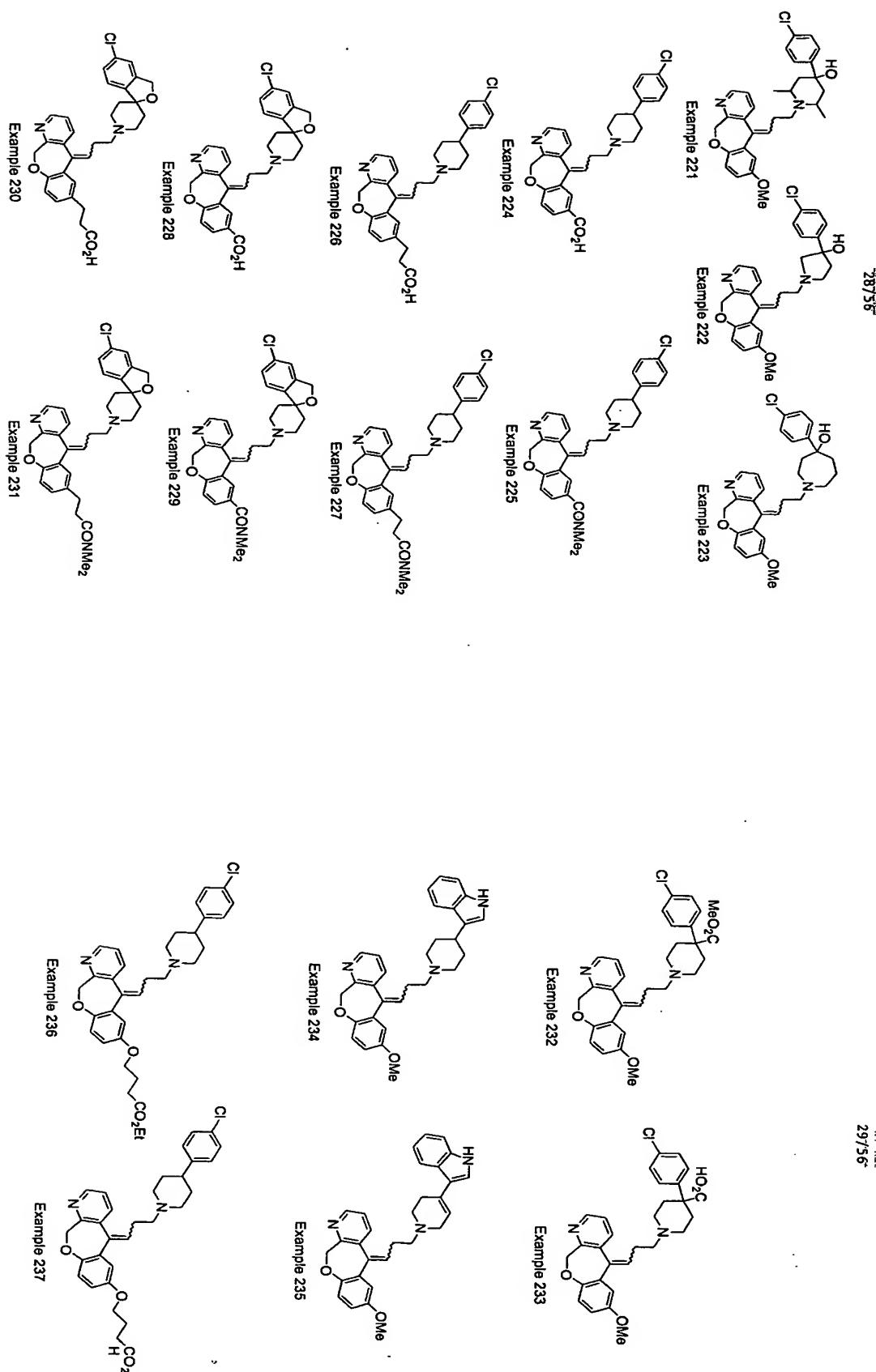
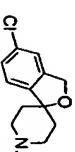


Figure 6W

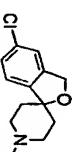
Figure 6X

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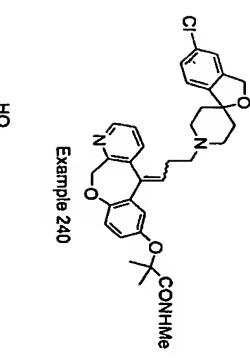
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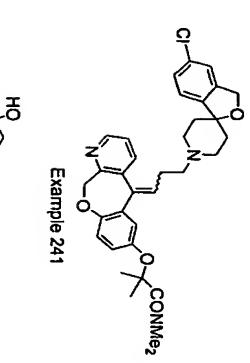
Example 238



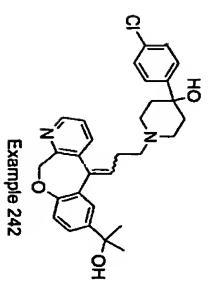
Example 239



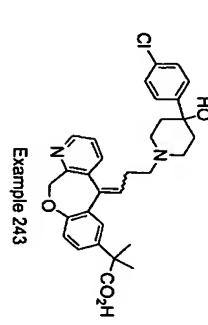
Example 238



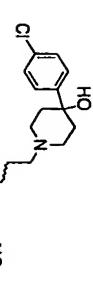
Example 239



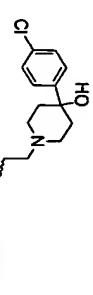
Example 240



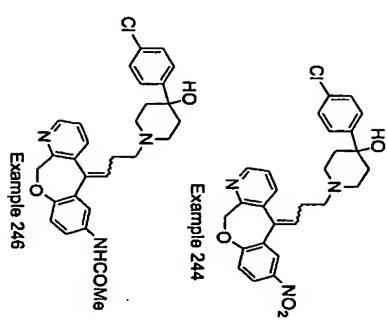
Example 241



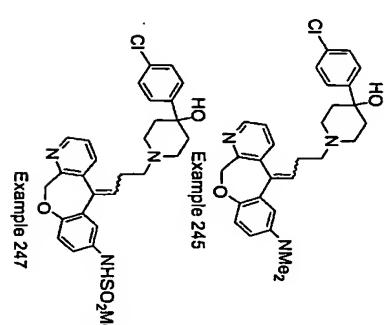
Example 242



Example 243



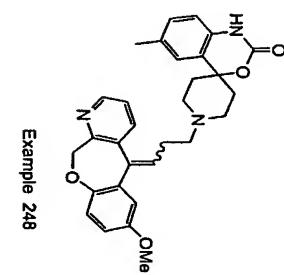
Example 244



Example 245



Example 246



Example 248

Figure 6Y

Figure 6Z

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Figure 7

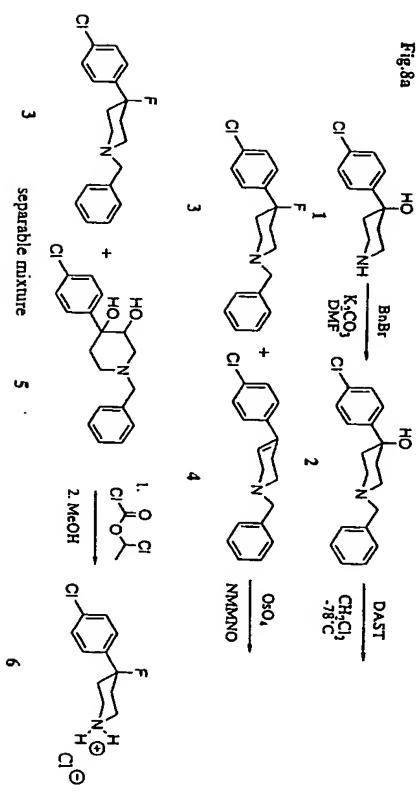
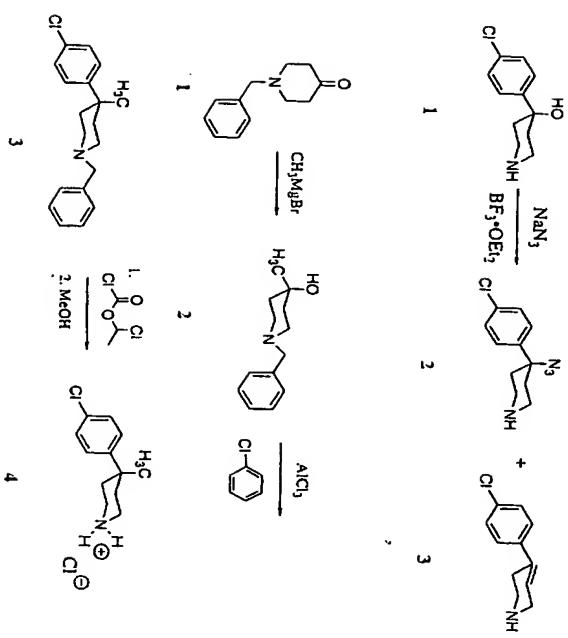


Fig. 8c



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Fig. 9a



Fig. 9b

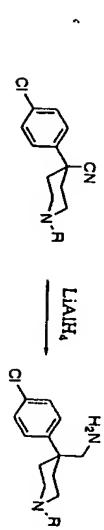


Fig. 9c

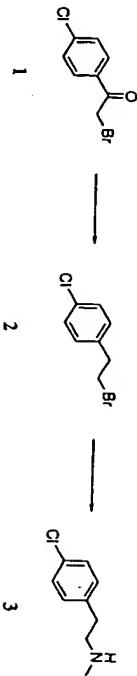


Fig. 9d

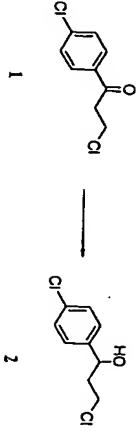


Fig. 9e



Figure 10a

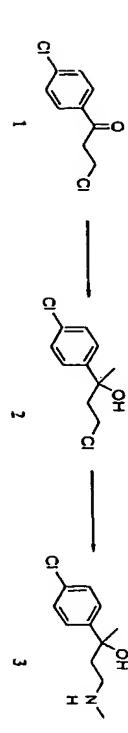


Figure 10b

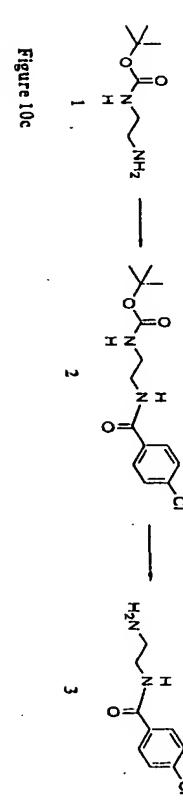


Figure 10c

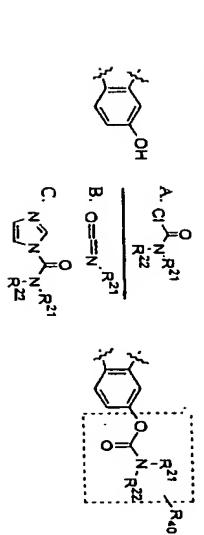
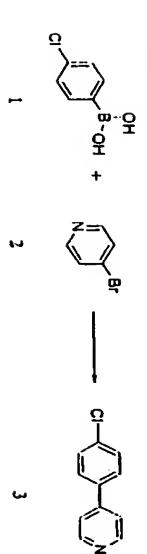


Figure 10 d



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WO 01/09138

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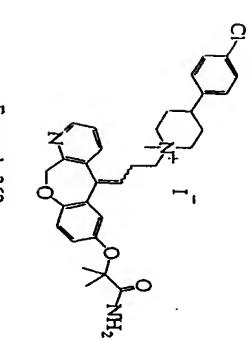
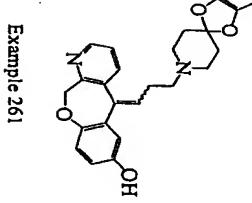
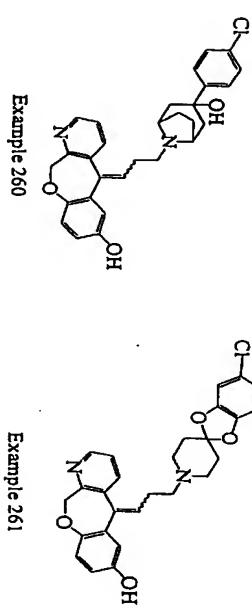
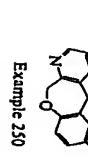
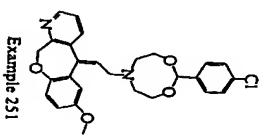
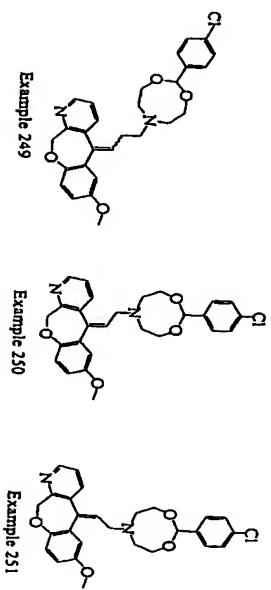


Figure 11B

Figure 11A

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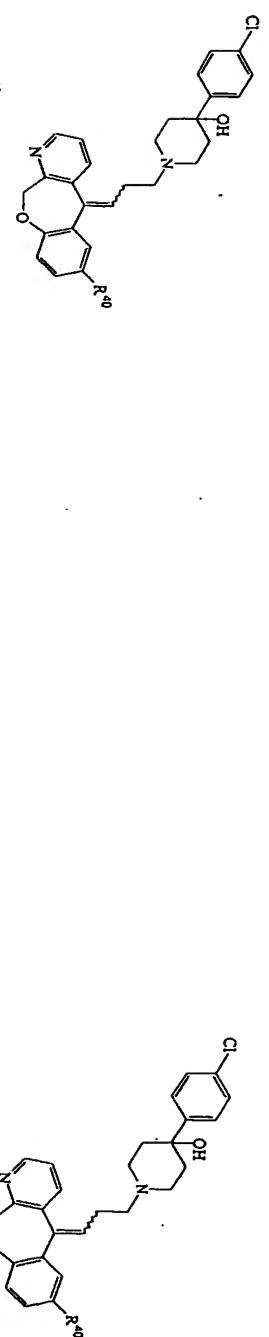


Figure 11C

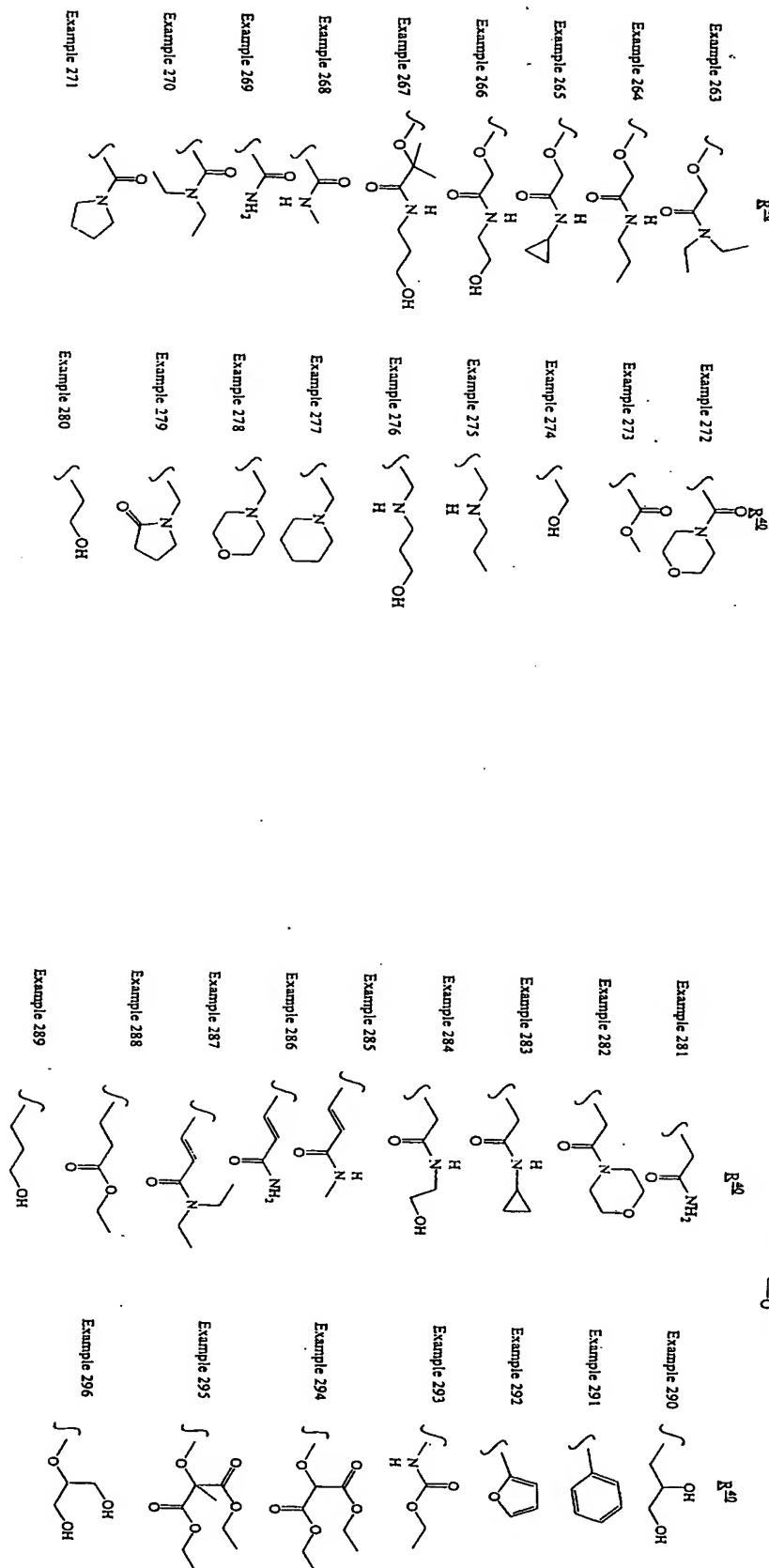


Figure 11D

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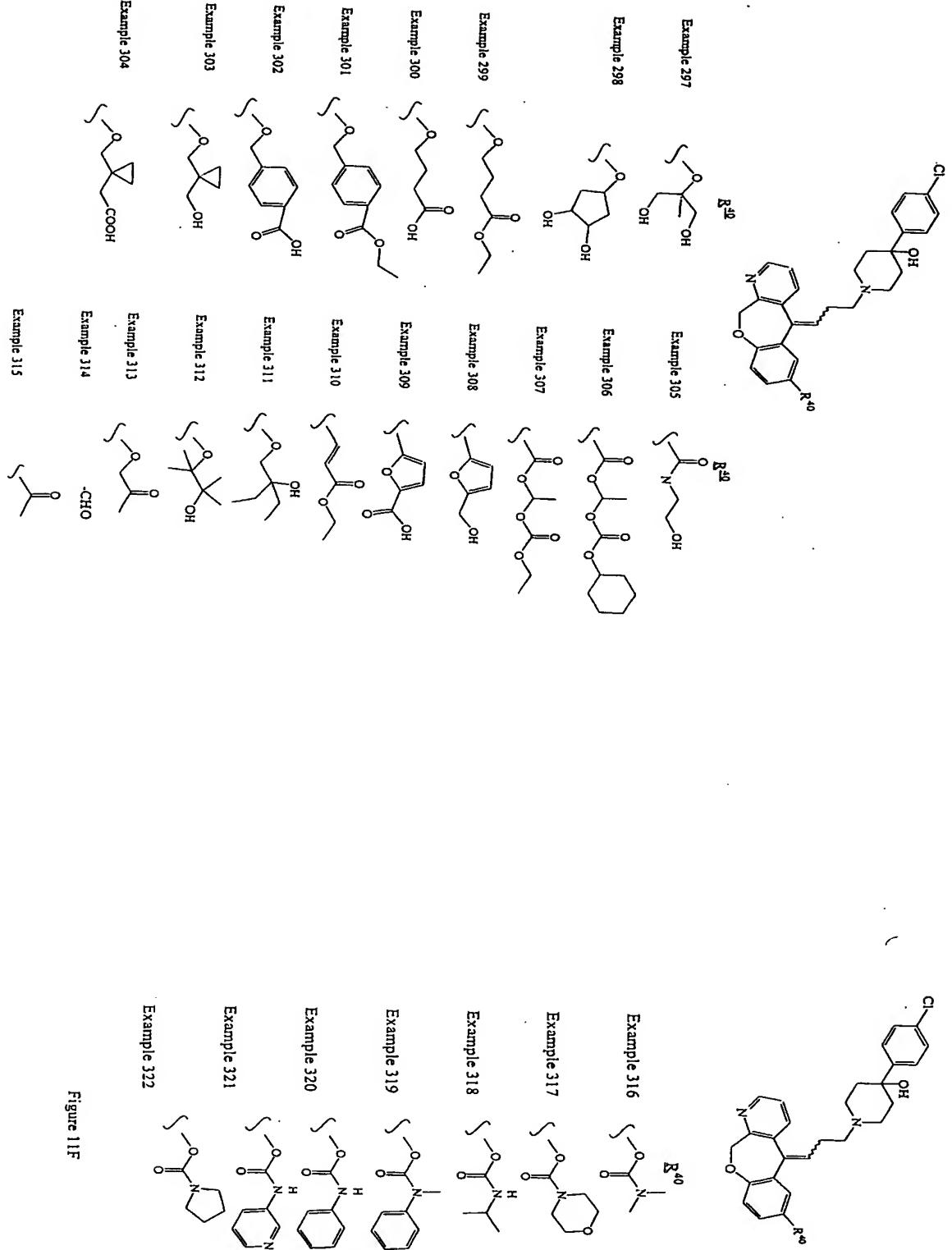
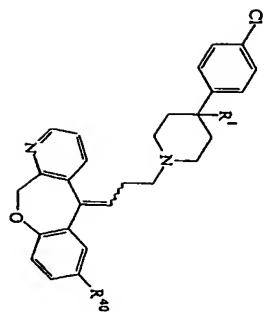


Figure 11E

Figure 11F

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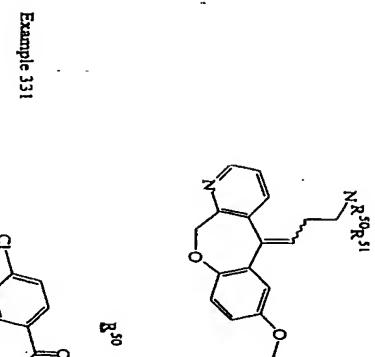
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R^1
-CN
 R^{40}

-OCH₃
 R^{40}

-OCH₃
Example 331



R^{50}
-H

R^{51}
-H

R^{50}
-CH₃

R^{51}
-CH₃

R^{50}
-OH

R^{51}
-OH

R^{50}
-CH₃

R^{51}
-CH₃

R^{50}
-OH

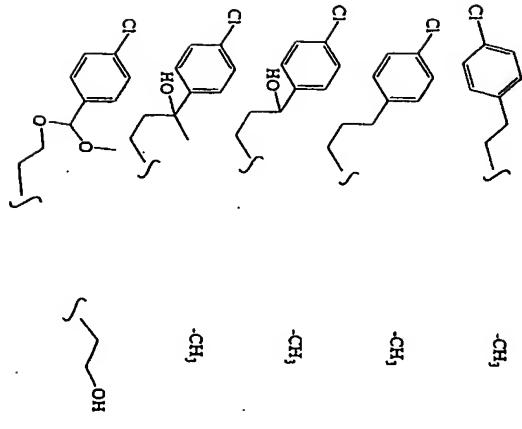
R^{51}
-OH

R^{50}
-CH₃

R^{51}
-CH₃

R^{50}
-OH

R^{51}
-OH



R^{50}
-CH₃

R^{51}
-CH₃

R^{50}
-OH

R^{51}
-OH

Figure 11G

Figure 11H

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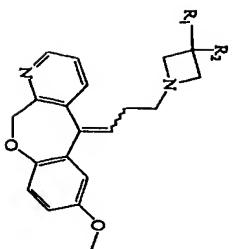
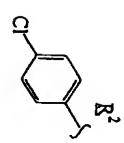
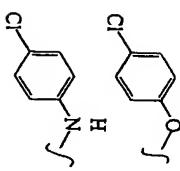
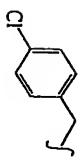
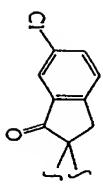
Example 338
-OHExample 339
-HExample 340
-HExample 341
-OHExample 342
-

Figure 111

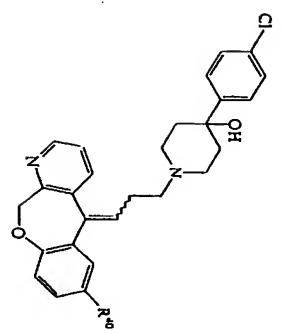
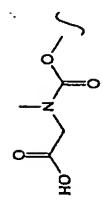
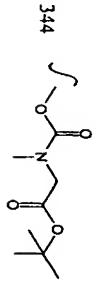
Example 343
 R^{40} Example 344
 R^{40} 

Figure 11J

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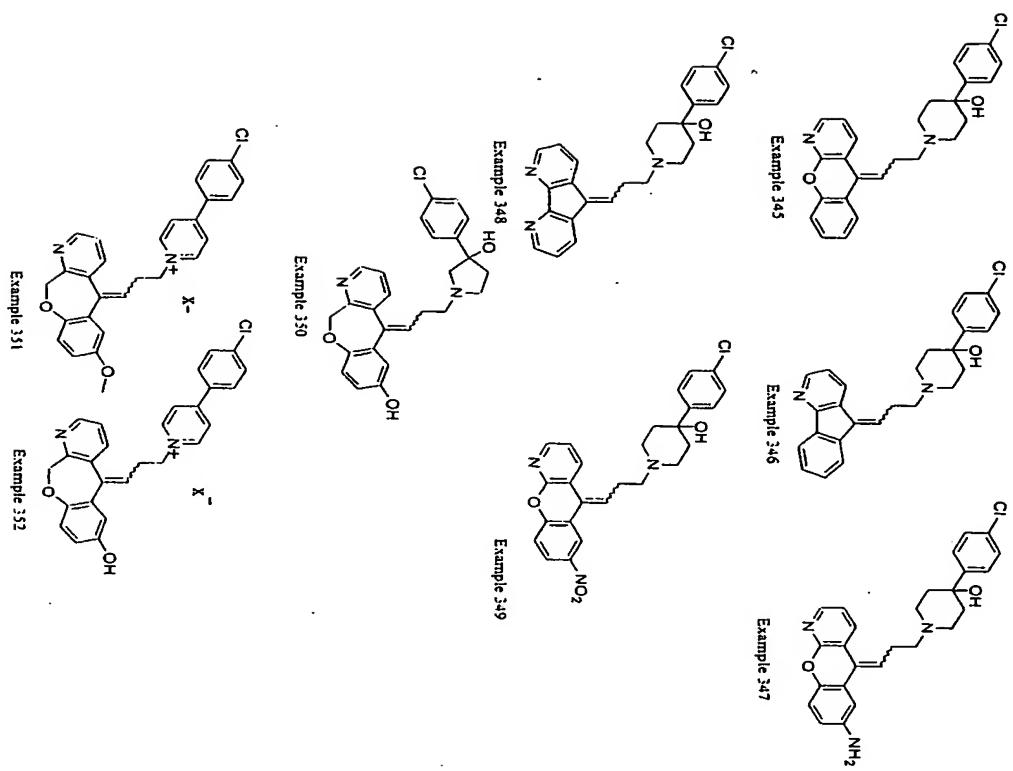


Figure 11K

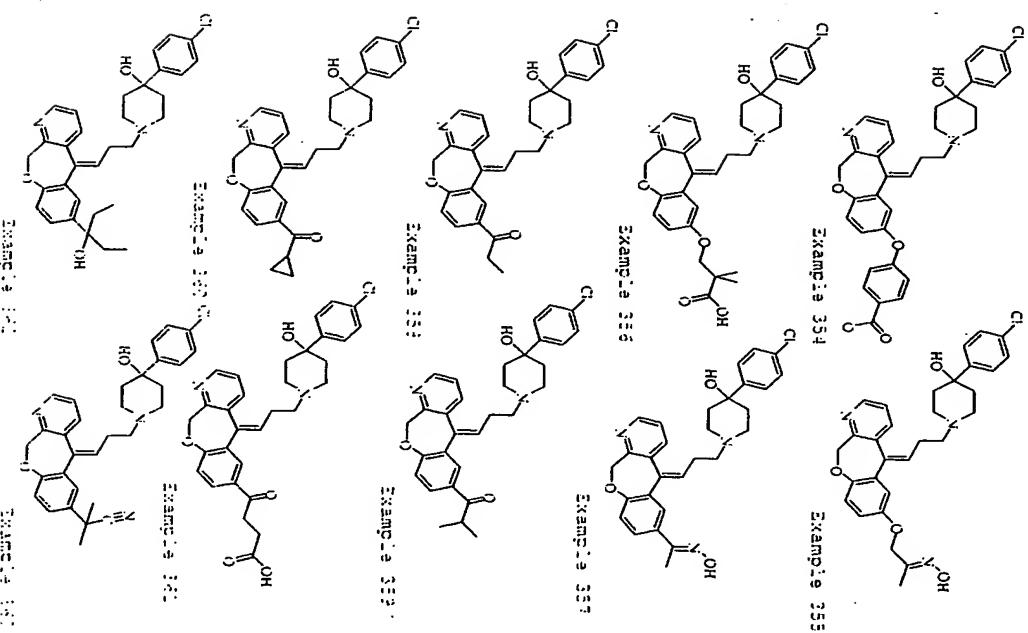
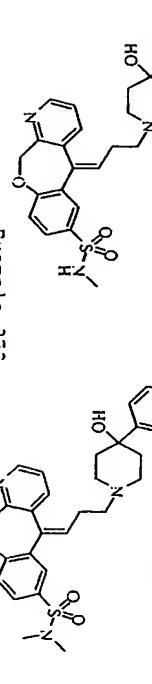
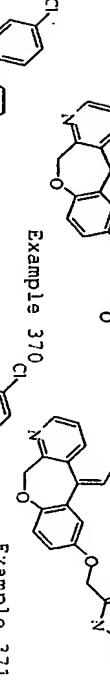
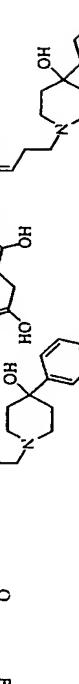
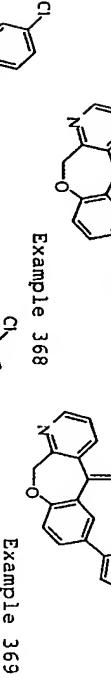
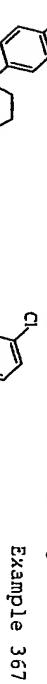
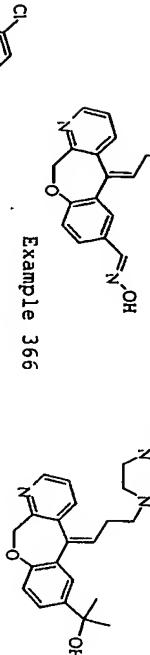
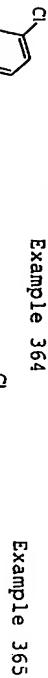
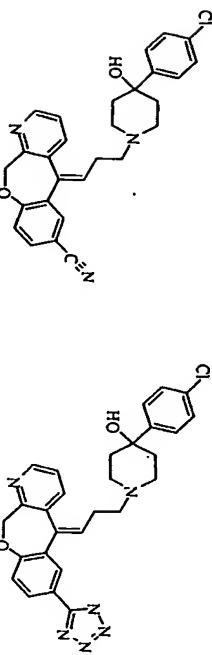


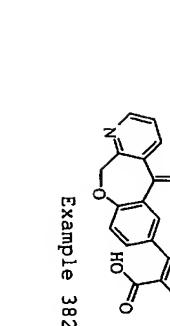
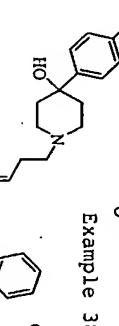
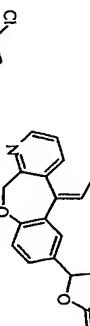
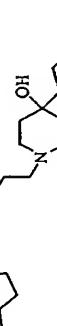
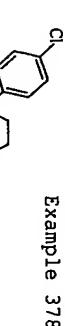
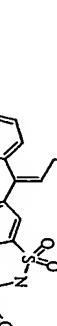
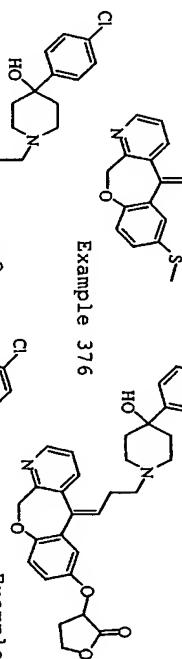
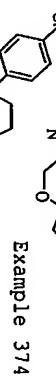
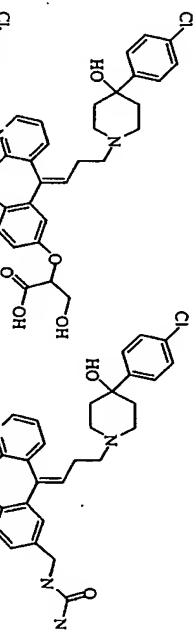
Figure 11L

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Example 373



Example 383

Figure 11M

Figure 11N

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Example 384

Example 385

Example 394

Example 395

Example 386

Example 387

Example 396

Example 397

Example 388

Example 389

Example 398

Example 399

Example 390

Example 391

Example 400

Example 401

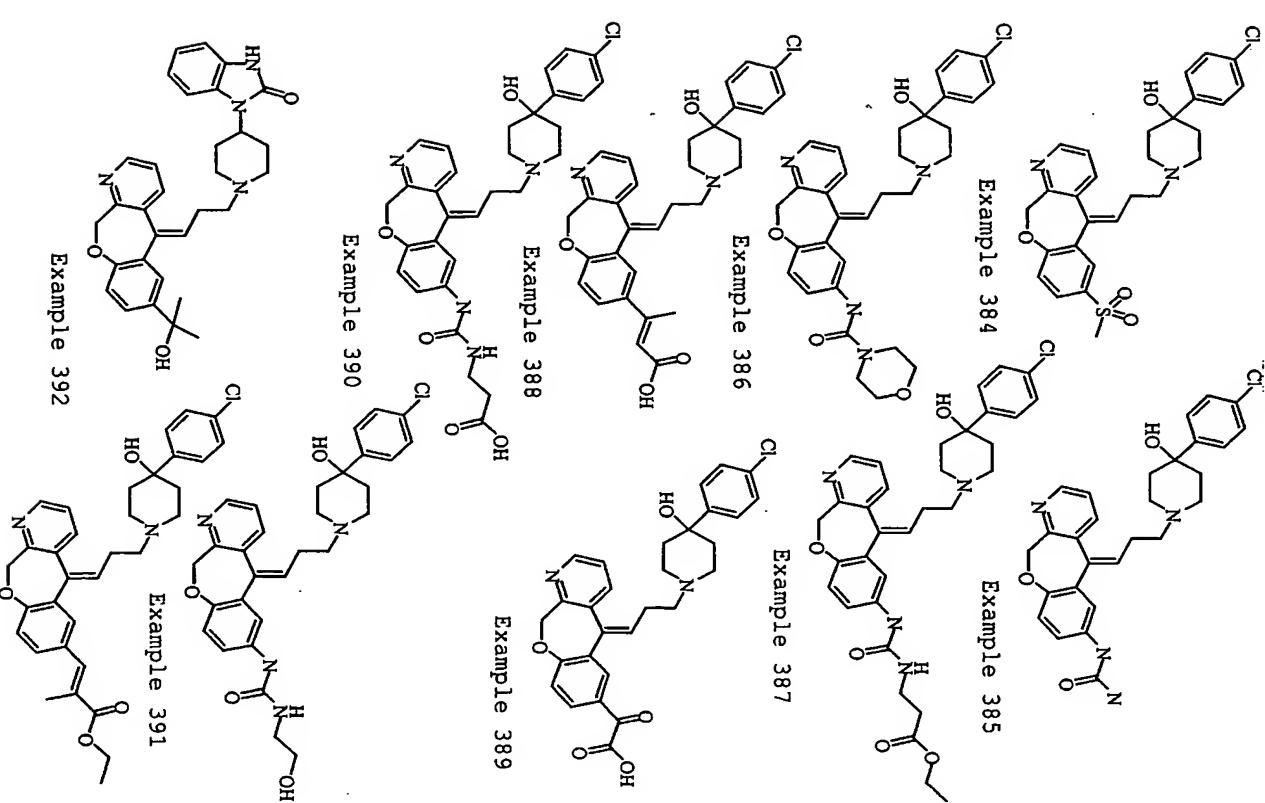


Figure 110

Example 392

Figure 11P

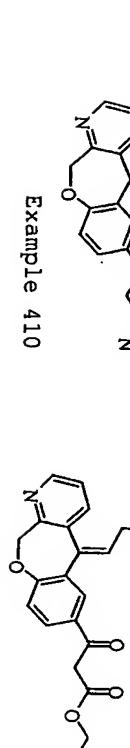
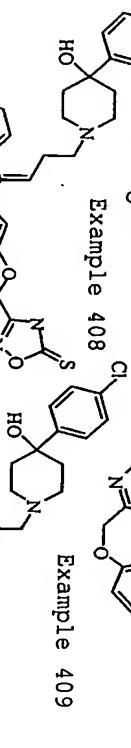
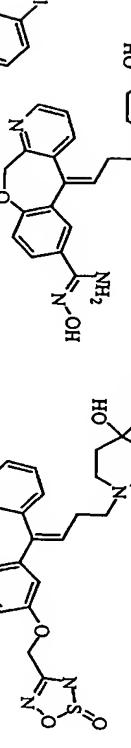
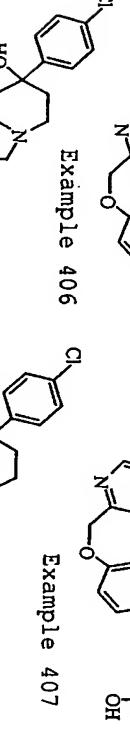
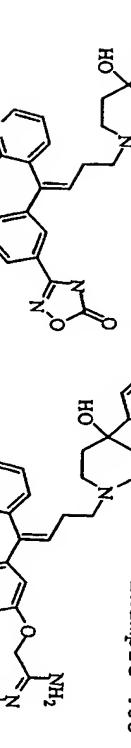
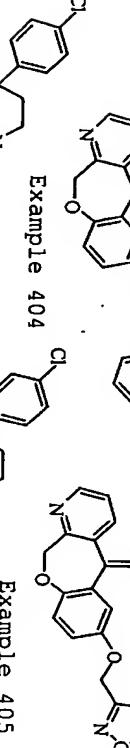
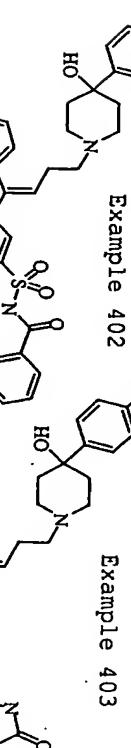
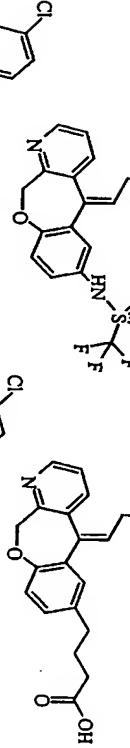
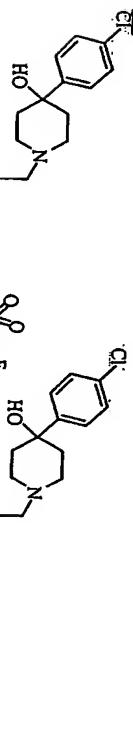
Example 393

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Example 411

Figure 11Q

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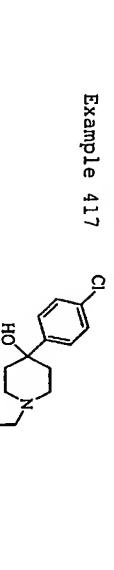
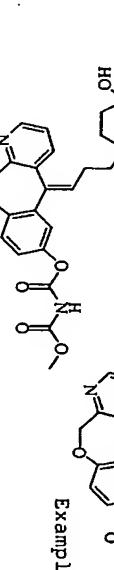
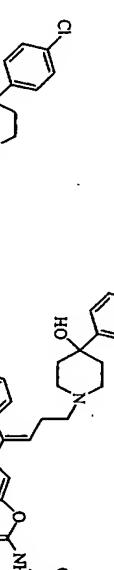
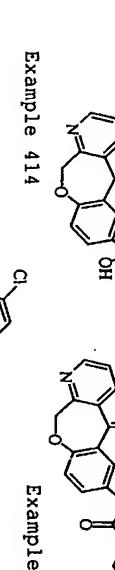
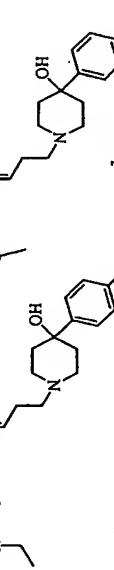
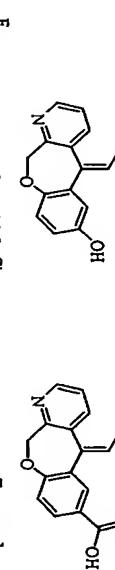
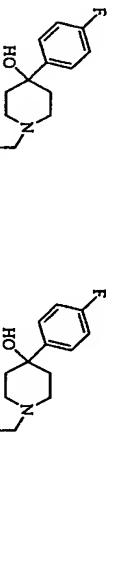


Figure 11R

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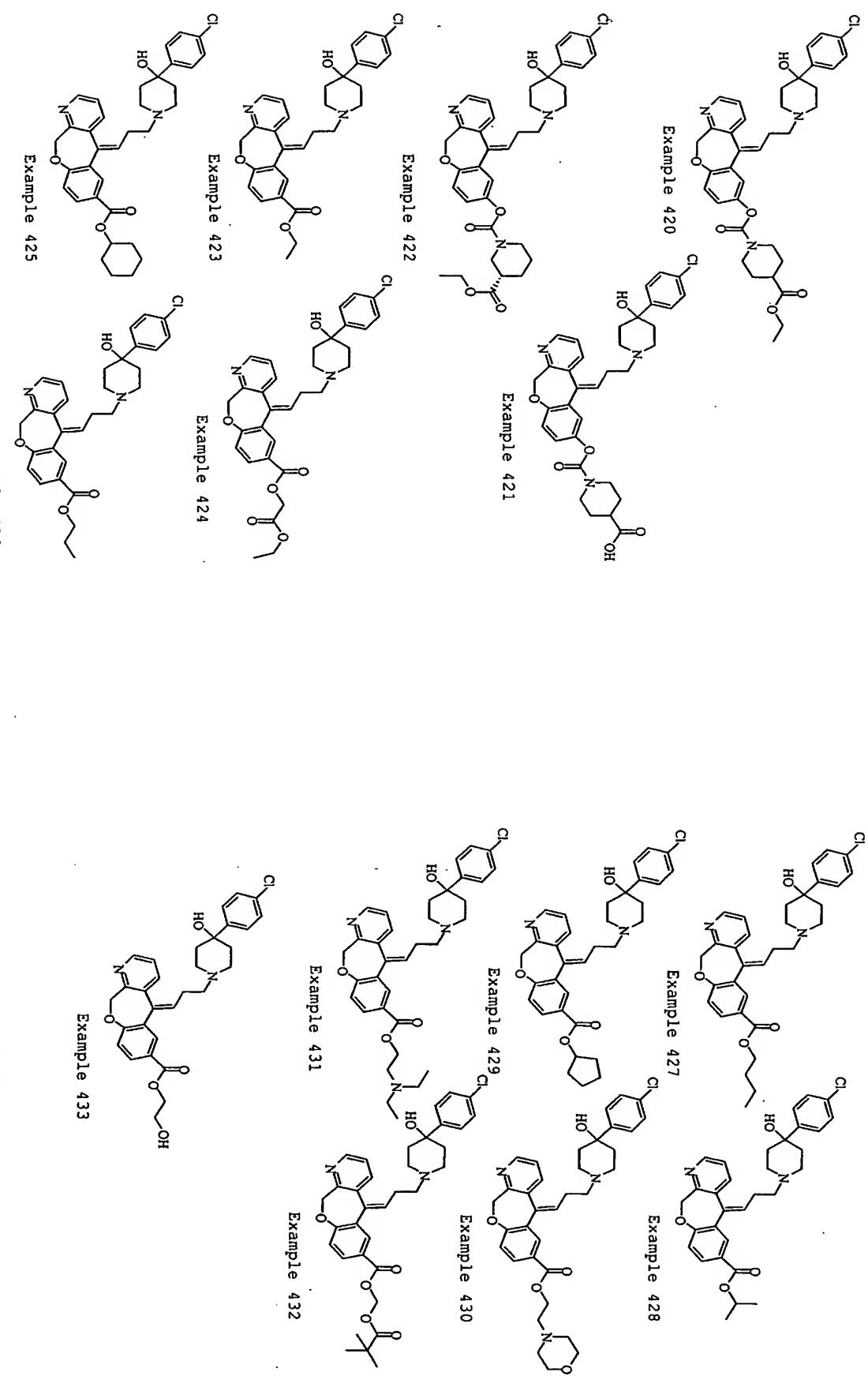


Figure 11T

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Figure 12

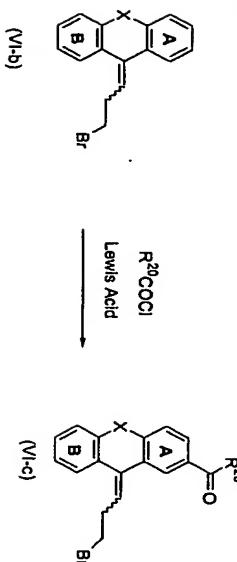
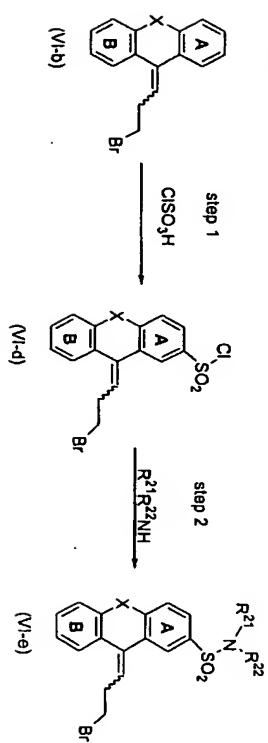


Figure 13



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(71) Applicants: MILLENNIUM PHARMACEUTICALS, INC., 1000 Stile Street, Cambridge, MA 02139 (US), KYOWA HAKKO KOGYO CO., LTD. (JP/JP); Shizuka 411 (JP), KOTERA, Onuma, 1188 Shimoura, Nagano, Nagano-cho, Sunagawa, Shizuka 411 (JP). For two-letter codes and other abbreviations, refer to the "Guidelines Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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Published:
— with international search report

(88) Date of publication of the international search report:
13 September 2001

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Category		Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
X		WO 92 16226 A (SMITHKLINE BEECHAM CORP) 1 October 1992 (1992-10-01) claims 1 and 9 (fluipentixol, clozapine), page 1, paragraphs 2 and 3		1,38
A		WO 97 44329 A (TEIJIN LTD) 27 November 1997 (1997-11-27) claims 1,9		1,38
P,X		WO 99 37651 A (LEUKOSITE) 29 July 1999 (1999-07-29) Whole document		1,38

Further documents are listed in the continuation of box C.

Patient family members are listed in annex.

- * Special categories of cited documents:
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- *⁹ document published prior to the international filing date but published on or after the international filing date
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- *¹¹ document referring to an oral disclosure, uses, exhibition or other means
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Date of the actual compilation of the International Search Report

15 January 2001

10.04.2001

Name and mailing address of the ISA

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Date of mailing of the International search report

8th document member of the same patient family

WO 01/09138 A3

(34) Title: CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR

(57) Abstract: Disclosed are novel compounds and a method of treating a disease associated with alveolar leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by (I) or (II) and physiologically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

National Application No.
PCT/US 00/20732

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 to 37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

International Application No. PCT/US 00/20732

FURTHER INFORMATION CONTINUED FROM PCT/US/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 - 22, 24-34, 38-59, 61-71 (all of them partially)

Compounds of claim 38 where X1 is a bond and their use

2. Claims: 1-22, 24-34, 38-59, 61-71 (all of them partially)

Compounds of claim 38 where X1 is -O- or -S-, and their use

3. Claims: 1-22, 24-34, 38-59, 61-71 (all of them partially)

Compounds of claim 38 where X1 is -CH₂-, -CH₂-CH₂-, -CH=CH-, and their use

4. Claims: 1-75 (claims 1-22, 24-34, 38-59, 61-71, partially)

Compounds of claim 38 where X1 is -CH₂-S-, -S-CH₂-², -O-CH₂-, -CH₂-O-, -SO-CH₂-, -CH₂-SO-, -S(O)2-CH₂-, -CH₂-S(O)2-

5. Claims: 1-22, 24-34, 38-59, 61-71 (partially)

Compounds of claim 38 where X1 is -NRC-CH₂-, -CH₂-NRC-, -NRC-CO-, -CO-NRC-

4. No required additional search fees were timely paid by the applicant, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-22, 24-34, 38-59, 61-71 (all partially)

Remark on Patent

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Search Application No
PCT/US 00/20732

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 92/16226 A	01-10-1992	NONE	
WO 97/44329 A	27-11-1997	JP 9309877 A AU 3135497 A EP 0914319 A	02-12-1997 09-12-1997 12-05-1999
WO 99/37651 A	29-07-1999	AU 2311999 A EP 1019700 A	09-08-1999 08-11-2000